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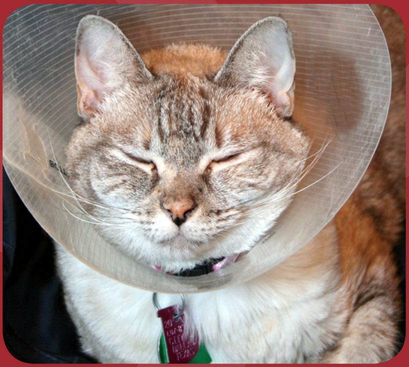
Proceedings 383



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Speaker Profiles

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Greg graduated from the University of Queensland in 1983. After spending 10 years in general practice he completed his Membership of the Australian College of Veterinary Scientists in Small Animal Surgery. Greg completed his 3-year residency in Dermatology and became a Fellow of the College in Veterinary Dermatology in 1997.

Since 1999 Greg has been a director of the Skin, Ear and Allergy Service at the Melbourne Veterinary Specialist Centre. Since 2002, he has been the Principle Fellow in Dermatology at the University of Melbourne in addition to taking responsibility for teaching of dermatology in the veterinary faculty.

Greg has authored and co-authored numerous articles in both Australian and international journals and presented both in Australia and at international conferences.

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Mandy graduated from Murdoch University Veterinary School in 1985 and completed a pathology and internal medicine residency at the same institution. She became a Member of the Australian College of Veterinary Scientists in Canine Medicine in 1991. She underwent a dermatology residency training program with Dr Ken Mason in Brisbane in 1993 and following her residency she became a Fellow of the Australian College of Veterinary Scientists in Veterinary Dermatology in 1998. Mandy is the Director of the Dermatology clinic at Murdoch University, a registered specialist and consultant in veterinary dermatology and an adjunct lecturer in dermatology at Murdoch University Veterinary Hospital teaching undergraduate 4th and 5th year veterinary students and the dermatology unit of the Masters degree for veterinary post graduate students at both Murdoch University and Massey University, New Zealand. She lectures veterinary students, veterinarians and veterinary nurses in dermatology at both national and international scientific meetings. She is currently the Assistant Chief Examiner and serves on the Board of Examiners and is the Secretary of the Dermatology Chapter of the Australian College of Veterinary Scientists, the Board of the Journal of Veterinary Dermatology and is the Oceanic representative for the World Veterinary Dermatology Association. She has extensive experience with clinical dermatology in companion animals and she likes teaching dermatology to veterinary undergraduate and postgraduate students

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Peter Hill graduated from the University of Liverpool in 1986 and spent five years in small animal practice before moving to the USA to undertake a residency in veterinary dermatology at the University of Wisconsin-Madison. In 1993, he returned to the UK and completed a PhD on mast cell biology at the University of Edinburgh, followed by a further eight years as lecturer and then senior lecturer in veterinary dermatology. In 2005, he moved to the University of Bristol where he combined clinical, teaching and research activities. In 2009, Peter moved to Australia to join the team at the Veterinary Specialist Centre in Sydney. He is the only veterinary dermatologist in the world to have been board certified in the UK, Europe and the USA as well as having a PhD. He has trained 9 dermatology residents, published over 65 scientific publications, given over 200 invited talks and presentations, is a former editor of the journal Veterinary Dermatology, and has written the textbook "Small Animal Dermatology: A Practical guide to the Diagnosis and Management of Skin Diseases in Dogs and Cats." In 2007, he was voted the best lecturer and clinical teacher by 4th and 5th year veterinary students.

Arthur House BSc BVMS PhD Cert SAS Dip ECVS MRCVS
Melbourne Veterinary Specialist Centre
70 Blackburn Road
Glen Waverley VIC 3150

Graduated from Murdoch University in 1994 and worked in general practice in Western Australia and then in the United Kingdom. Whilst in general practice Arthur achieved a Certificate in Small Animal Surgery with the Royal College of Veterinary Surgeons. In 2000 he began a residency in surgery at the Royal Veterinary College London. In 2004 Arthur successfully became a Diplomate of the European College of Veterinary Surgeons. Following his surgical training Arthur joined a research group to perform clinical research investigating genetic and immunological defects in Anal Furunculosis patients. During this research period Arthur maintained close ties with the clinical environment, continuing to work within a referral surgical environment. In 2008 Arthur's research resulted in him been awarded a PhD with the University of London. Following the PhD Arthur was awarded a position as a lecturer in Small Animal Surgery at the Royal Veterinary College.

Whilst working as a lecturer at the Royal Veterinary College he has worked in both the orthopaedic and soft tissue services, ultimately working exclusively within the soft tissue service. In July 2009 Arthur returned home to Australia and now works at the Melbourne Veterinary Specialist Centre, a multidiscipline referral hospital.

Arthur's specific interests are in minimally invasive surgery, particularly interventional radiology techniques, oncologic surgery and gastrointestinal surgery. Arthur continues to have research interests and presently is co-supervising PhD students investigating genetics and immune responses in inflammatory bowel disease as well as hepatic regeneration following attenuation of portosystemic shunts. Arthur has a broad range of publications not only as a result of his research in anal furunculosis but additionally clinical publications based on data from clinical cases and experience. Additionally Arthur has been an author in several textbooks, including BSAVA thoracic and ENT surgery, Textbook of surgical nursing and is presently working on chapters for the next BSAVA manual on the care of the post operative patient. Arthur lectures to vets regularly in the UK via RVC CPD (continuing professional development), BSAVA regional and at BSAVA congress. Additionally Arthur has provided lectures for CPAT (practitioners association of Thailand).

Richard Malik DVSc DipVetAn MvetClinStud PhD FACVSc FASM
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Veterinary Science Conference Centre B22, Regimental Crescent,
The University of Sydney NSW 2006

Richard graduated from the University of Sydney in January 1981. He completed a PhD in the Department of Pharmacology at the John Curtin School of Medical Research (ANU). Richard then moved to the Neurobiology Research Centre at the University of Sydney. In 1987 he returned to the Department of Veterinary Clinical Sciences as its first Resident in Small Animal Medicine. He then remained in the vet school in varying capacities for 16 years. Richard is currently the Valentine Charlton Specialist at the Centre For Veterinary Education. Richard passed his FACVSc in Medicine of Cats in 1991 and is a registered specialist in feline medicine and small animal medicine. Although interested in all facets of small animal medicine, he is particularly interested in infectious diseases, neurology, cardiology and genetically transmitted diseases. Recently he has become interested in the best way to feed cats for health and longevity and toxicological disorders of cats, especially permethrin toxicity. Richard has wide research interests, including mycobacterial infections and fungal disease (especially cryptococcosis). He is also interested in diseases of wildlife.

Beth McDonald BVSc (Hons) MVetClinStud MACVSc (Small Animal Medicine) DACVD
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Dr Beth McDonald graduated from the University of Sydney (Hons) in 1988. Prior to this Dr McDonald had extensive experience in the agricultural industry. In 1979-1980 she attended the C.B. Alexander Agricultural College, Tocal, in the Hunter Valley. She attained her Advanced Certificate in Agriculture, Dux. During her time at Tocal, she majored in sheep and cropping, with a special interest in wool production. After Tocal, she became the manager of a 400 acre beef property on the outskirts of Sydney. In 1982 she returned to Tocal College to manage their sheep section and tutor students. In 1983 she sat her HSC at TAFE and successfully gained entry into Veterinary Science. Throughout her undergraduate years she received numerous awards for excellence in clinical work and became President of the Veterinary Society. After graduation in 1988 Beth worked as a veterinarian at the North Shore Veterinary Hospital. During that time she completed, her Masters Degree in Veterinary Clinical Studies through Murdoch University and gained her Membership in Small Animal Medicine with the Australian College of Veterinary Scientists. In 1995 she began a residency in veterinary dermatology at the Louisiana State University in Baton Rouge, U.S.A. In 1998, she successfully completed her examinations and became a Diplomate of the American College of Veterinary Dermatologists. Since that time, Dr McDonald has worked as a registered specialist in Veterinary Dermatology. Her special interests include the management of allergic patients, demodicosis and ear disease. She consults at Kuringai Veterinary Hospital, the University of Sydney, city campus, the Animal Referral Hospital, and Canberra Veterinary Hospital. Dr McDonald regularly attends international conferences and is a member of the Dermatology chapter of the Australian College of Veterinary Scientists. Her close association with Tocal Agricultural College, where her passion for animals, education and dermatology began, has been maintained. In 1997, she became a member of the C.B. Alexander Foundation, a ministerial appointment, and has been closely involved with the development and support of agricultural education throughout NSW, with special focus on the disadvantaged. Beth and her daughters are volunteer members of their local surf life saving club. She has a food allergic, atopic Labrador that volunteers for any new treatment trials, especially dietary ones!

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A world renowned equine surgeon and dermatologist, Reg graduated from the University of Queensland in 1951, completing his fellowship with the Royal College London (1973), Australian College of Vet Scientists (1975) and gaining his Doctorate in Vet Science (1984). He founded the Oakey Veterinary Hospital in 1952, specialising in equine practice from 1966. Reg has published over 70 referred articles and is the author of five texts on Equine Dermatoses. He has held positions with the AVA, AEVA and ACVSc throughout his career and received distinguished awards including the Gilruth Prize (1986), T.G. Hungerford Award (1987), VMS Award Excellence in Veterinary Medicine (1987, 1988 & 2001), Member of the Order of Australia (1987), RIDIC Major Horse Industry Prize (1997), Australian Council of Professions, Queensland Professional of the Year (2001), and EVA Award for services to the Australian Horse Industries (2008).

David Robson BVSc (Hons), MACVSc (Canine Medicine) FACVSc (Dermatology)
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David graduated in 1992 from the University of Queensland. He worked in general practice for 6 years before spending the next decade in dermatology referral practice with the Animal Skin Ear and Allergy Clinic at the Melbourne Veterinary Specialist Centre. He gained his ACVSc Fellowship examination in dermatology in 2005. He has practiced clinical dermatology, published and lectured both in Australia and overseas. His current research interests include in vitro efficacy of ear cleaners, and antifungal resistance profiles of Malassezia spp.

David is a foundation member of the Australian College of Veterinary Scientists Dermatology Chapter.

Linda J. Vogelnest BVSc(Hons) MACVSc (Feline Medicine) FACVSc (Dermatology)
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University Veterinary Centre, Camden & Sydney
C08 - University Veterinary Centre, Camden
The University of Sydney NSW 2006

Linda is employed as Specialist Veterinary Dermatologist at University of Sydney (Camden & Sydney campuses) seeing small, large and exotic animal referrals. She graduated from Sydney University in 1984, and worked in private and university small animal practice in Australia and UK for over 10 years before following a long-time interest in Dermatology. Linda achieved Membership of Australian College of Veterinary Scientists in Feline Medicine in 1997, and undertook an alternative Dermatology Residency Program from 1997-2001 with the Australian College of Veterinary Scientists, supervised by Ralf Mueller together with Sonya Bettenay, Ken Mason, and Greg Burton. Linda achieved Fellowship of Australian College of Veterinary Scientists by examination in Veterinary Dermatology in 2003.

As a Specialist Veterinary Dermatologist at the University of Sydney, Linda's roles include running a busy dermatology consulting service, dermatology training at both under-graduate and post-graduate levels, involvement in research projects, and staying current with the dermatology literature. One of Linda's passions is teaching dermatology: she is involved in teaching undergraduate veterinary science students (lectures, and compulsory and elective clinical rotations), supervising final year Veterinary

Science Honour's research projects, and supervising post-graduate dermatology residency programs (Linda's first dermatology resident completed her 3-year training program, and her second resident has just commenced her training program).

Linda also enjoys lectures and presentations to general veterinary practitioners, and has also made numerous presentations at dermatology meetings in Australia and internationally. She also plays an active role in the Dermatology Chapter of the Australian College of Veterinary Scientists, and has been part of the Science Week Dermatology Stream program committee for the last 3 years. Her special dermatology interests include allergies in all species, dermatohistopathology, and skin surface cytology sampling. She has been involved in research projects involving intradermal testing in horses, and canine superficial pyoderma.

Program

WEDNESDAY, 17 FEBRUARY 2010

8.30 – 9.00	Registration
9.00 – 9.45	Logical diagnostic approach to equine or production animal skin disease *Linda Vogelnest*
9.45 – 10.30	Alopecic and crusting skin diseases **-** Part 1: Diagnosis and treatment guidelines *Linda Vogelnest*
10.30 – 11.00	Morning Tea
11.00 – 11.30	Alopecic and crusting skin diseases **-** Part 2: Diagnosis and treatment guidelines *Linda Vogelnest*
11.30 – 12.00	Diagnostic approach to nodular dermatoses *Reg Pascoe*
12.00 – 12.30	Sarcoids: Treatment guidelines *Reg Pascoe*
12.30 – 1.30	Lunch
1.30 – 2.15	The itchy horse: Diagnosis *Linda Vogelnest*
2.15 – 3.00	Qld itch & atopic dermatitis: Treatment options *Linda Vogelnest*
3.00 – 3.15	Afternoon Tea
3.15 – 4.15	Pastern Dermatitis: Approach to diagnosis and management *Linda Vogelnest & Reg Pascoe*
4.15 – 4.45	Interactive case session *Linda Vogelnest & Reg Pascoe*
4.45 – 5.00	Closing Remarks

THURSDAY, 18 FEBRUARY 2010

8.30 – 9.00	Registration
9.00 – 9.45	Introduction: Dermatology – that was then and this is now *Greg Burton*
9.45 – 10.30	Anatomy and Pathology of the Ear *Linda Vogelnest*
10.30 – 11.00	Morning Tea
11.00 – 11.45	Pathogenesis, Diagnosis and Principles of Management of Otitis: Part 1 *Greg Burton*

11.45 – 12.30	Pathogenesis, Diagnosis and Principles of Management of Otitis: Part 2 *Greg Burton*
12.30 – 1.30	Lunch
1.30 – 2.15	Antimicrobial Therapies in Otitis *David Robson*
2.15 – 3.00	Ear Cleaning Techniques *David Robson*
3.00 – 3.15	Afternoon Tea
3.15 – 4.00	Surgical Options in Otitis *Arthur House*
4.00 – 4.45	Interactive Case Session *Greg Burton, Linda Vogelnest, David Robson & Arthur House*
4.45 – 5.00	Closing Remarks

FRIDAY, 19 FEBRUARY 2010

8.30 – 9.00	Registration
9.00 – 9.45	Pruritus: Differential Diagnoses and Diagnostic Approach: Part 1 *Mandy Burrows*
9.45 – 10.30	Pruritus: Differential Diagnoses and Diagnostic Approach: Part 2 *Mandy Burrows*
10.30 – 11.00	Morning Tea
11.00 – 11.45	Atopic Dermatitis: Pathophysiology and Principles of Management *Greg Burton*
11.45 – 12.30	Advances in Topical Therapies in the Management of Atopic Dermatitis *Greg Burton*
12.30 – 1.30	Lunch
1.30 – 2.15	Management of Infections in the Atopic Dog *Beth McDonald*
2.15 – 3.00	Allergy Testing and Immunotherapy *Peter Hill*
3.00 – 3.15	Afternoon Tea
3.15 – 4.00	Feline Allergic Skin Disease *Peter Hill*
4.00 – 4.45	Interactive Case Session *Mandy Burrows, Peter Hill, Greg Burton & Beth McDonald*
4.45 – 5.00	Closing Remarks

SATURDAY, 20 FEBRUARY 2010

8.30 – 9.00	Registration
9.00 – 9.45	Skin Biopsy: How, Why, Where and Interpreting the Results: Part 1 *David Robson*
9.45 – 10.30	Skin Biopsy: How, Why, Where and Interpreting the Results: Part 2 *David Robson*
10.30 – 11.00	Morning Tea
11.00 – 11.45	Recent Advances in Dermatological Diseases and Therapies - Dogs *Beth McDonald*
11.45 – 12.30	Recent Advances in Dermatological Diseases and Therapies - Cats *Mandy Burrows*
12.30 – 1.30	Lunch
1.30 – 2.15	Feline Mycobacterial Disease Update *Richard Malik*
2.15 – 3.00	Canine Demodicosis: Recent Advances *David Robson*
3.00 – 3.15	Afternoon Tea
3.15 – 4.00	Zoo Animal Dermatology: An Exercise in First Principles Workups *Greg Burton & Linda Vogelnest*
4.00 – 4.45	Interactive Case Session *Greg Burton, Linda Vogelnest, Beth McDonald, Mandy Burrows & Peter Hill*
4.45 – 5.00	Closing Remarks

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Chapter 1

Diagnostic Approach to Equine and Production Animal Skin Disease

Linda J. Vogelnest
BVSc MACVSc FACVSc

INTRODUCTION: SPECIAL FEATURES OF SKIN DISEASE

As the largest body organ and being readily visible and accessible, the skin has some great advantages over other body organs. In particular, early recognition of disease, ready examination and sampling, and monitoring response to therapy are much easier than with many other body organs. The most common causes of skin disease in domestic animals, including horses and production animals, include infectious diseases (bacterial, fungal, and parasitic), hypersensitivities, environmental diseases (solar, toxic, nutritional), and neoplasia. Despite the variety of aetiologies, there are only limited ways skin can respond to disease, which means many different diseases may appear similar or the same. The most appropriate treatment options for skin disease vary with the aetiology, and it is not unusual for diseases with similar clinical appearance to have widely varying treatment needs. Being an exposed epithelial surface with normal resident micro flora, the frequent occurrence of impaired barrier function and subsequent secondary infections or moisture loss, and potential difficulties with readily identifying true pathogens over normal flora, further complicate many skin diseases. When managing skin disease it is therefore vital to make use of all the advantages this great organ provides, to carefully look for clues and always work towards making a definitive diagnosis.

EQUINE AND PRODUCTION ANIMAL SKIN DISEASE

Although a similar variety of diseases can occur in both horses and production animals, there is a marked difference in the tendency of owners to seek veterinary attention. With economics typically far more important for all but the most valuable of production animals, mild diseases, particularly affecting few animals, are rarely presented. Diseases that are severe, and affecting multiple or valuable animals are the typical one's presented for veterinary advice. In contrast, many horses are used for purposes where their skin and coat appearance are important, and a higher level of veterinary intervention is often sort for individual horses. A logical approach to skin disease, aiming to confirm a diagnosis is equally important for both groups.

TREATMENT PRINCIPLES FOR SKIN DISEASE

1. Always aim to confirm a diagnosis before considering treatment. This is especially vital for severe or chronic diseases, but ideal for all skin diseases. By having a good basic knowledge of the common skin diseases, and following basic principles this is often not as difficult as one may imagine!

2. Treat specifically for the disease confirmed, or to clearly exclude major differential diseases where confirmation is not readily possible in other ways. There are a range of treatment options for many skin diseases, with variable response rates and potential side effects, so a working knowledge of the most commonly used drugs in dermatology is vital.

3. Symptomatic therapy is important at times for patient comfort while awaiting test results or response to treatment trials. Most importantly, symptomatic treatment should be used intelligently, particularly with chronic or recurrent disease: ideally use monotherapy in a treatment trial manner, so response to that treatment is more readily evident. For example, response to antibiotics and glucocorticoids administered concurrently doesn't tell which of these products was effective, and it is very rare for both to be necessary! Explain to owners your treatment aims, that response to symptomatic treatments may be variable, and encourage them to contact you to discuss response; all of which will ultimately help determine a better long-term management plan for chronic diseases.

DIAGNOSTIC APPROACH TO SKIN DISEASE

Diagnosis for skin disease is most readily obtained by following a logical, ordered diagnostic approach. There are four important initial diagnostic steps:

a) Collect a detailed history

b) Perform a complete physical examination: whole body and detailed skin examination, accurately describing the clinical lesions

c) Formulate a prioritised differential diagnosis list

d) Logically progress to the most helpful diagnostic tests/treatment trials to distinguish between the major differential diagnoses

1. History

There are often many helpful diagnostic clues from owners that are important for prioritizing differential diagnoses. For severe, chronic or recurrent diseases a client questionnaire is invaluable to facilitate collection of a thorough history (see copy at end of notes). The most important questions include:

a) The presenting complaint

MAJOR PRESENTING COMPLAINTS

Most Common	**Less Common**
Pruritus	Coat changes
Alopecia +/- scaling	Crusting
Nodules	Ulceration
Swelling +/- Discharge	Depigmentation
Pastern dermatitis	Poor wound healing

It is often helpful diagnostically to categorise diseases into groups dependent on their typical presentations, often reflected in the presenting complaint. For example, the most common typically pruritic skin diseases include hypersensitivities, and some mite infestations (e.g. sarcoptes, trombiculids), while alopecic and/or scaling diseases with less notable pruritus include dermatophytosis, dermatophilosis, and many external parasitic diseases in large animals (lice, chorioptes). It is important however to remember that most diseases can present in variable ways, so to avoid discounting a disease in an atypical presentation it is important to remain alert for other key diagnostic clues. For example, dermatophytosis is typically associated with mild or no pruritus, however should be an important differential for well-demarcated areas of alopecia, even when notably pruritic, especially at trauma-sites e.g. girth, tack-contact sites.

b) Signalment: age, breed, sex

Age is often a helpful guide, with some diseases more common in young (many infectious diseases), young adults (hypersensitivities), or in older animals (neoplasia). There are some diseases linked more commonly to certain breeds: good dermatology texts are a valuable guide for this, however internet access and search engines (e.g. google) are often helpful when used discerningly, and may be more current.

Sex predispositions are less common.

c) Time factors: age of onset, duration, progressive/recurrent, previous disease

In horses these details are sometimes unknown or vague due to changing ownership, however are very helpful for guiding diagnosis. A number of diseases tend to be recurrent, including hypersensitivities, and some infectious diseases (e.g. dermatophilosis). Some diseases tend to wax and wane in severity (hypersensitivities, pemphigus foliaceus). Owners sometimes don't link previous skin diseases with current signs and don't offer diagnostically helpful information readily (e.g. a horse with regular bouts of hives, now presents with a pruritic dermatitis unassociated with hives: suggesting hypersensitivities (airborne, food, insect) are important differentials.

d) Initial lesions: types + sites

By the time animals are presented to the veterinarian, initial or transient lesions may no longer be present, and the disease may be now masked by secondary infections or self-trauma lesions, however descriptions of initial lesions from astute owners can at times be very helpful clues. Were the lesions (e.g. alopecia) present prior to onset of pruritus? (suggestive of alopecic rather than pruritic skin diseases). And were initial areas of hairloss well-demarcated (suggesting primary alopecia, due to hair follicle destruction or damage) or poorly demarcated and associated with pruritus? (suggestive the alopecia is secondary to self-trauma).

e) Pruritus: presence + degree

This is very useful information when accurately supplied; however mild to moderate pruritus may be poorly appreciated by some owners not having prolonged contact with their animals (i.e. mild to moderate pruritus may only be evident when the animal is at rest, and not when stimulated by feeding/exercise/interaction etc.)

f) Previous treatment: drugs, response

In addition to previously prescribed treatments, a myriad of "remedies" are often used by equine owners in particular, and may mask initial lesions and/or produce new lesions unassociated with the initial disease (e.g. contact irritant or allergy reactions).

g) Regular routine: bathing, insect control, diet, use of rugs

These details will at times be very relevant to some differential diagnoses, and are important to obtain. Rugs are often used very frequently in horses, and skin surface and/or rug hygiene may be poor; excessive or inappropriate rugging can be the cause of many skin diseases presenting with scaling and patchy alopecia.

h) General health

Sometimes there is a tendency to focus too closely on readily evident lesions, while forgetting to examine the rest of the animal and checking on general health and any history of disease. Animals with recent or chronic ill-thrift will be more likely to suffer from infectious agents (e.g. dermatophytosis, dermatophilosis), diseases associated with immunosuppression (e.g. demodicosis), or potentially from systemic diseases (e.g. systemic lupus erythematosus).

2. Physical Examination

A thorough and detailed skin examination and a full physical examination should both be performed. In particular a careful search should be made for primary lesions (caused directly by the disease process), which are often less obvious and may be very sparse, as these are the most useful diagnostically (both descriptively and as diagnostic sampling sites). Secondary lesions are typically far more prevalent, produced by secondary factors including self-trauma, medications, and secondary infections, and are the least useful diagnostically.

Clinical Lesions

There is a defined vocabulary to accurately describe skin lesions that is important to use for guiding potential diagnoses, to clearly indicate to other vets involved with cases, or when referring back to records at a later time. Both type and location of lesions are important to note, along with a knowledge of which lesions are typically primary or secondary (Note: some lesions may be either primary or secondary e.g. alopecia). A detailed list of skin lesions is included at the end of these notes. The most relevant of these lesions are briefly introduced below:

Primary lesions

- Papule - small, solid, palpable elevation of skin up to 1cm diameter; may be caused by inflammation, hyperplasia, or neoplasia
- Wheal - small, transient circumscribed elevation filled with oedema; will pit with digital pressure
- Pustule - small, circumscribed white-topped elevation, filled with pus
- Vesicle - small, circumscribed fluid-filled elevation of epidermis; >1cm = bulla; fragile and transient

Secondary lesions (Non-specific; some may be primary at times)*

- Alopecia* - hair loss: partial to complete; well-to-poorly demarcated
- Scale* - accumulation of loose fragments of stratum corneum (outermost layer of epidermis)
- Erythema - redness
- Hyperpigmentation - increased pigmentation due to increased melanin deposition
- Lichenification - thickening and hardening of skin, characterised by an exaggeration of superficial markings
- Erosions & ulcers - partial & complete (respectively) loss of epidermis
- Crusting - dried exudate, serum, pus, blood, cells on surface of skin
- Comedones - dilated hair follicle filled with debris: “blackhead”
- Epidermal collarettes - circular lesion with peripheral rim of scale, erythema – remnant pustule

3. Formulate a Prioritised Differential Diagnosis List

This third step in a logical diagnostic approach to skin disease is the most vital. Before rushing on to diagnostic tests, take time to consider the information you have gathered in the first two steps (i.e. history and physical examination), and make a list of the more likely differentials, prioritized from most to least likely. When more comfortable and familiar with evaluating skin diseases, this step is often done at least partially while collecting the initial history, prompting further historical questions that may help distinguish between the major differentials even before the clinical examination is performed. It is important to keep an open mind while assessing all details, and not allow your diagnostic approach to be biased by pre-conceived ideas or initial thoughts. At times there may be conflicting details, suggesting contrasting diagnoses, in which case all major diagnoses should remain on the differential list.

4. Plan Diagnostic Tests most likely to help confirm a diagnosis

Faced with your prioritised differential diagnosis list, you should then plan the most likely tests to help distinguish between the differentials. Additionally, simple non-invasive tests that exclude even less-likely differentials will often be ideally performed initially.

The major diagnostic tests used in equine and production animal dermatology include:

a) Skin Scrapings

Skin scrapings are predominantly indicated for external parasitic infections, primarily mites. They can be used to search for dermatophytes; although trichograms or tape preparations, containing more hair shafts, are generally higher yield tests for animal dermatophytes. When scraping for mites, it is important to think about *which* mites you are testing for: scrapings should be superficial for surface mites (majority of mites affecting horses), and deep for deep dwelling mites, especially demodex (very rare in horses and production animals). With superficial scrapings, the aim is to collect ample scale and surface debris over wide areas (e.g. 5cm^2) and/or multiple sites to maximise yield of potentially sparse mites. Paraffin oil is placed on the skin, a scalpel blade (sharp or blunted; No. 10 or 20) is angled to gently scrape the skin surface, and oil and surface scale are transferred onto a glass microscope slide. Superficial scrapings do not need to produce surface bleeding. For deep skin scrapings the skin should be squeezed and scraped repeatedly to produce capillary oozing, to ensure mites are extruded from the hair follicles where they reside. Areas with papules and/or excessive scaling may give a higher yield of mites. A cover slip is placed on top of the sample to provide a uniform surface for examination, and samples examined microscopically with 4X or 10X lens (40X or 100X magnifications).

b) Surface Skin Cytology

Surface cytology samples are simple, fast, and useful for identifying infectious agents (bacteria, fungi, and some mites), inflammatory cell types, immune-mediated disease clues (e.g. acantholytic cells in pemphigus) and occasionally neoplastic cells. They tend to be greatly under utilised in veterinary practice. Dry skin lesions are best sampled with acetate tape preparations (e.g. Scotch® tape, or plain, non-patterned clear tape), pressed firmly sticky-side down onto lesional skin. Initial gentle cleansing with water, saline or very dilute chlorhexidine scrub is important to clear surface debris from dusty coats of many large animals (in contrast to tape sampling with many dogs and cats), or multiple samples should be collected and initial samples discarded. Tape preparations are useful for evaluating superficial bacterial folliculitis, dry forms of dermatophilosis, and dermatophytosis. They can be Diff-quik® stained (the fixative should not be used as the adhesive is dissolved and the sample clouded; give 6 x 1 second dips in the pink and then the blue Diff-quik® stains), or a few drops of the blue Diff-quik® stain alone (or other blue stain such as methylene blue) can be placed under the tape, then the stain gently smeared by wiping on top of the tape using a tissue to create a flat even surface for examination. Oil can be placed directly onto the tape surface for oil immersion examination, necessary to view bacteria.

Direct impression smears are effective for moist lesions. After initial cleaning of surface debris with saline or water, a glass slide is pressed firmly onto the affected area.

Impression smears and tape preparations should be examined for the presence of inflammatory cells, bacteria, fungi or neoplastic cells. Tape preparations can also be examined for broken hair shafts containing fungal hyphae and/or spores, and appear to be a very sensitive method for many cases of dermatophytosis.

Scanning with the 4X or 10X lens is important initially to identify areas of inflammation when present, then oil immersion (1000X) is required for bacterial examination, while 40X will reveal larger fungi and cell morphology.

Special techniques may be required for some organisms (e.g. maceration of crusts for *Dermatophilus* spp.). Crusts and/or surface scale should be soaked in warm saline for 15 minutes, then smeared onto a glass slide, dried, and Diff-quik® stained. Typical rows of parallel zoospores, producing classical "railroad track" appearance, are usually readily seen, even in dry forms of disease.

Nodular lesions can be sampled with fine needle aspirates; using a 10ml syringe and 25-21g hypodermic needle (smaller gauge in more vascular nodules), with gentle suction and needle redirection within the lesion. The aspirated sample (often in the hub of the needle) is gently sprayed onto a glass slide. Slides from impression smears and aspirates should be air-dried and stained (e.g. Diff-quik® often sufficient; Gram, Giemsa, or Methylene blue sometimes indicated). As for skin surface cytology, scanning under low power for suspect or heavily cellular areas, and close evaluation under high powers (40 and 100X lens) is important to search for infectious agents.

c) Deeper skin cytology

Nodular lesions can be sampled with fine needle aspirates; using a 10ml syringe and 25-21g hypodermic needle (smaller gauge in more vascular nodules), with gentle suction and needle redirection within the lesion. The aspirated sample (often in the hub of the needle) is gently sprayed onto a glass slide. Slides from impression smears and aspirates should be air-dried and stained (e.g. Diff-quik® often sufficient; Gram, Giemsa, or Methylene blue sometimes indicated). As for skin surface cytology, scanning under low power for suspect or heavily cellular areas, and close evaluation under high powers (40 and 100X lens) is important to search for infectious agents.

d) Trichogram

A trichogram can be useful to evaluate some hairloss disorders (e.g. alopecia areata, dermatophytosis, demodicosis). Hairs are plucked from the periphery of alopecic lesions, and laid carefully onto 2-3 drops of paraffin oil on a glass slide. The proportions of hairs in telogen (rest) and anagen (active growth) phases can be estimated, important to some follicular growth diseases (e.g. anagen defluxion); and hairs examined for shaft abnormalities (e.g. alopecia areata), parasites or fungal elements. Samples do not require clearing with potassium hydroxide (KOH), as the vast majority of veterinary dermatophytes are ectothrix fungi (live on the outside of hair shafts) unlike the common human dermatophytes (endothrix; within hair shafts).

e) Microbial Culture

Microbial isolation and antimicrobial sensitivity testing is often important for deep microbial skin infections, particularly with more unusual or resistant bacteria (e.g. *Nocardia*) and with most fungi. The specific culture indicated can sometimes be guided by cytology results prior to histopathology results being available. Skin biopsies collected with sterile technique are ideal for all deeper lesions. A detailed history and differential diagnoses should be provided to the laboratory, as special techniques and culture media are required for some organisms. While waiting for histopathology results where the aetiology remains unknown, fresh sterile skin biopsies supplied on saline moistened swabs can be stored refrigerated by the laboratory, and the most appropriate culture techniques employed when results available.

Fungal culture is indicated for all cases of suspect or confirmed dermatophytosis, to indicate the species involved, potential source of origin, and risks of contagion. Plucked hairs and scraped scale should both be collected, and ideally samples from large animals are sent to the laboratory for testing, as special media may be needed. Microbial culture is more problematic with superficial skin infections, as normal skin flora or transient contaminants may interfere with results and/or be pathogens; and is less commonly indicated (see individual diseases). Interpretation of microbial culture results can be misleading, as negative cultures will not always exclude infectious disease, and positive cultures may not always indicate organisms responsible for disease. Culture results are one potential piece in a diagnostic pathway, and must be combined with clinical and historical data, cytology findings and often histopathology for correct interpretation.

f) Wood's Lamp Examination

This test can be useful in small animals to detect dermatophytosis, however is only occasionally useful in large animal disease. Wood's light examination may reveal green fluorescence along hair shafts, indicating dermatophyte infection of those hairs, but will only be positive for some dermatophyte species (50% of Microsporum canis, M. equinum, and rarely others). It is important to warm up the lamp for 10-15-minutes prior to use to attain maximum fluorescence. Wood's lamp fluorescence is commonly over interpreted: bright apple-green fluorescence along the hair shafts is a positive result; yellow apparent fluorescence is common with many scaling or pigmented lesions and is a negative result.

g) Skin Biopsies

Skin biopsies for histopathology are an important diagnostic tool in skin disease, although often misused. They should only be considered after formulation of a differential diagnoses list based on historical and clinical data, and after surface cytology tests are performed. Biopsies are not indicated simply faced with chronic disease of unknown aetiology, where secondary infections, self-trauma lesions, and drug effects may mask primary changes; nor with many superficial skin diseases, including hypersensitivities, where a non-specific perivascular mononuclear and/or eosinophilic dermatitis is common. Biopsies are most useful with deep dermal and nodular diseases, and unusual or extensive unexplained lesions. Secondary infections should ideally be treated before biopsy collection. Samples should be collected carefully, with *no prior skin surface disinfection*, and using delicate handling to avoid artifactual damage. Biopsies may be collected using local or regional anaesthesia (2% lignocaine, placed subcutaneously beneath lesions), or occasionally general anaesthesia for difficult areas (e.g. coronary bands, face) or more fractious animals. A range of lesions should be collected; primary lesions whenever present (e.g. pustules, papules), and differing secondary lesions (e.g. crusts, alopecia, hyperpigmentation, scale). *A minimum of 4 samples, and ideally 6-8 should be collected.* Punch biopsies are useful for uniform lesions, papules, small pustules, and crusts, and 8mm punch biopsies should be used for the vast majority of samples collected from horses. Elliptical excisions are preferable for transitional regions (e.g. border of normal and abnormal), larger pustules/bullae/vesicles, and deep lesions. Samples should be blotted dry, thin samples pressed gently onto a piece of cardboard to prevent curling, and immersed in 10% buffered formalin. The biopsy defects can be closed with one or two simple interrupted or cruciate sutures, usually of non-absorbable suture material. *To attain maximum information from the histopathology report, it is vital to provide the pathologist with relevant history, a description of clinical lesions, and your differential diagnosis list.* A histopathologist with a special interest or qualifications in skin (dermatohistopathology) will often provide more useful information.

h) Specialised Tests

Specialised tests are required for evaluating some diseases, in particular hypersensitivities. ***Intradermal testing*** is useful for managing atopic dermatitis, although it *does not* confirm this diagnosis as false positive and negative reactions can occur. Results are used for formulating immunotherapy ("allergy vaccines"). Serum "allergy" testing, measuring allergen-specific

IgE levels, is the next best option for formulating immunotherapy however some tests have very poorly repeatable results and specificity. Currently the serum allergen-specific IgE test preferred by most veterinary dermatologists in Australia is the Allercept® test developed by HESKA in USA, available through Gribbles Pathology. It detects species specific IgE via the high-affinity IgE episolon (ε) receptor, giving it higher specificity than many previous tests. They offer an equine specific IgE Allercept®, which appears to give fairly accurate results. False positives and negative will still occur, and the intradermal test remains the gold standard. Allergen-specific IgE testing is a useful option where referral to a veterinary dermatologist for intradermal testing is declined by owners. ***Patch testing*** is required to firmly diagnose contact allergies.

Diagnostic treatment trials, including ***insect control trials***, ***elimination diets***, and occasionally symptomatic treatment trials are also essential diagnostic tools for dermatology.

EQUINE/PRODUCTION ANIMAL SKIN QUESTIONNAIRE

OWNERS NAME:		**ANIMALS NAME:**	
BREED:		**AGE:**	
SEX:		**GELDED? (Y/N):**	

1. What is the main problem?
2. How long ago did it start?
3. What time of year? spring summer autumn winter
4. How long have you owned this animal?
5. Do you know of any prior history of skin disease? (give details)
6. Where on the body did the current problem start?
7. What did the affected area first look like? red/inflamed; scurf/dandruff; scabs/crusty; hairloss; swelling; lumps/nodules; small bumps/papules; other
8. Is the problem static; waxing and waning; or progressive?
9. If chronic, is the problem constant all year roundor intermittent? If changing, when does it seem better e.g. summer, winter? Is it completely better at any time?
10. Is there itch? Specifically, does he/she rub the face/head; bite at belly or legs; rub back; rub base of tail; rub mane; shake the head; other areas of irritation?
11. If there is itch, was it seen first; or were skin changes noticed first?
12. Do you know of any relatives of your animal? If yes, do they have a history of skin problems? (give details)
13. Is your horse in contact with or nearby other horses or animals? Number of horses in direct contact. List numbers and types of other animals. Is grooming equipment shared?
14. Do any in contact animals have skin problems?
15. Is your horse normally rugged? with hood? How often? How long for each day? At what time of year? Type of rug?
16. Does your horse go to shows/events/races? How often?
17. Where is your horse kept? Stables; paddock; yards; other. Give details e.g. many trees; grass only; bare ground; other.
18. Does your horse get worse in any particular situation e.g. when riding; when hot; in certain paddocks; when rugged; when not rugged; other.
19. Does your horse have a history of other diseases or problems?
20. Is your horse currently well? If no, give details.

21. What is current diet? List any supplements given? Does diet change during the year?
22. What topical shampoos or other products are used regularly? How often?
23. Please list any previous treatments for the skin problem and if they helped or caused side effects:

TREATMENT	**RESPONSE**	**SIDE EFFECTS**

24. When were the last cortisone preparations used: lotions/creams; tablets; injections
25. What medications are being used now?
26. What insect control and worming products are used regularly, and how often?

PRIMARY SKIN LESIONS

1. Papule

- Small solid elevated lesion up to 1cm diameter; palpable; major portion projects above the plane of surrounding skin
- May be due to localised hyperplasia of epidermis or dermis e.g. Wart, localised dermal infiltrates – inflammatory, neoplastic or metabolic deposits e.g. Calcium
- Can vary in colour:
    - Red – superficial bacterial folliculitis, scabies, insect bites
    - Black or brown – malignant melanoma, basal cell carcinoma
    - Purpuric – vasculitis
- May be follicular and non-follicular

2. Pustule

- Circumscribed raised lesion containing purulent exudate e.g. Pus composed of leucocytes +/- cellular debris +/- bacteria
- Vary in size, shape, and colour – latter depending on contents (white, yellow, to green); most commonly contain neutrophils (yellow colour) and are infectious, occasionally eosinophils, may be sterile
- May be intraepidermal, subepidermal or follicular in location
- Abscesses = larger and deeper (s/c) accumulations of pus, not visible on skin surface

3. Plaque

- Flat-topped elevation, occupying a relatively large surface area in comparison to height above surface
- May form from confluence of papules, localised dermal infiltrates e.g. Oedema, from rubbing

4. Macule/Patch

- circumscribed flat coloured lesion; any shape, macule up to 1cm diameter, patch > 1cm diameter
- may occur due to:
    - epidermal hyperpigmentation (increase in melanin) e.g. post inflammatory
    - epidermal hypopigmentation (loss of melanin) e.g. vitiligo
    - dermal pigmentation (vascular abnormalities e.g. capillary dilatation - erythema, or purpura - local haemorrhage); range from petechiae (pinpoint <1cm diameter through ecchymoses - larger bruise-like >1cm diameter {extravasated red blood cells: redness will not clear with pressure}
    - cutaneous infarct = area of cutaneous necrosis due to occlusion of blood vessels e.g. vasculitis, bacterial embolism have variegated dusky red greyish hue, irregularly shaped, sometimes slightly depressed below surface

5. Nodule

- palpable, solid, round or ellipsoidal; extends into deeper layer of skin and larger than a papule (>1cm diameter)
- 5 main types:
    - epidermal: e.g. papillomatosis (warts)
    - epidermal-dermal: e.g. melanoma, invasive scc
    - dermal: e.g. urticaria, sarcoid
    - dermal-subdermal: e.g. panniculitis
    - subcutaneous: e.g. lipoma
- in dermis may occur with systemic disease – inflammation, neoplasia, metabolic deposits, insect bites, viral/bacterial infections
- tumour: can be used to describe larger nodules
- descriptive terms for nodule appearance can vary markedly: e.g. hard, firm, soft, fleshy, warm, movable, fixed, e.g. surface: smooth, keratotic, ulcerated, fungating

6. Wheal

- round or flat-topped elevated papule or plaque, characteristically evanescent, disappearing within hours
- epidermis not affected, no scaling
- borders sharp but not stable; variation in shape - round, oval serpiginous, annular
- may be tiny papules (3-4mm diameter) to giant plaques (10-12cm)
- pale red +/- white in center when severe due to pressure compression of vessels; occur with oedema in upper dermis
- will blanch with diascopy (glass slide pushed firmly onto surface)
- indicate hives or urticaria; angiodema = huge hive on distensible regions e.g. lips, eyelids

7. Vesicle and Bulla

- rarely seen as fragile and transient
- circumscribed, elevated lesion containing fluid; vesicle < 0.5cm, bulla > 0.5cm diameter
- can be intra or subepidermal
- seen with viral, autoimmune or irritant dermatoses

PRIMARY OR SECONDARY SKIN LESIONS

1. Alopecia

- May be partial (diffuse or patchy) or complete
- May be primary e.g. Alopecia areata; or secondary to e.g. Trauma or inflammation

2. Scale

- Abnormal shedding or accumulation of stratum corneum as flakes
- Normal epidermis replaced every 27 days for humans, 22 days for dogs, ? For horses – end product = cornified cell of stratum

corneum, packed with filamentous proteins, normally no nucleus, usually lost imperceptibly

- Increased rate of epidermal cell production and/or decreased rate of cell loss produces increased scale (dandruff)
- Can have follicular scale (follicular casting) = excess follicular scale adherent to hair shafts

3. Crusts

- Hardened deposits from blood, serum or pus drying on skin surface; also scales or medications
- May be thin, delicate and friable, or thick and adherent
- Yellow if from serum; green or yellow-green from purulent exudates; brown or dark red from blood e.g. Trauma

4. Pigmentary Changes

- Hypopigmentation = leukoderma (skin) or leukotrichia (hairs) – due to loss of melanin e.g. Vitiligo, damage to basal cell layer e.g. Discoid lupus erythematosus
- Hyperpigmentation – due to increased melanin e.g. Post inflammatory hyperpigmentation; typically a secondary change
- Coat colour changes – can occur from hair follicle abnormalities e.g. Follicular dysplasia, externally applied substances e.g. Bleaching shampoos, metabolic processes/toxins e.g. Copper deficiency (cattle)

5. Comedones

- Dilated hair follicle filled with cornified cells and sebaceous material
- May predispose to bacterial folliculitis
- May be 2° to seborrhoea, due to occlusion with greasy medications, or from systemic, topical or adrenal steroids
- May be 1° - demodicosis or dermatophytosis

SECONDARY SKIN LESIONS

1. Erosions

- Moist, circumscribed, usually depressed lesion formed with loss of all or some of epidermis
- Frequent with pruritic diseases; may see extensive areas with bullous diseases e.g. Bullous pemphigoid
- Do not scar unless become secondarily infected

2. Ulcer

- Hole in skin with destruction of epidermis and at least part of superficial dermis
- Occur due trauma, tissue infarction: large or small vessel occlusion/constriction e.g. From emboli, thrombi, cryoagglutinins

3. Scar

- Area of fibrous tissue that has replaced damaged dermis; may be hypertrophic or atrophic, sclerotic or hard
- Occurs following ulceration, reflecting healing pattern
- Scarred epidermis is thin, generally without normal skin lines and appendages

4. Epidermal collarette

- Special scale arranged as circular rim of loose keratin flakes (peeling keratin)
- Remnants of the roof of a pustule, papule, or rarely vesicle or bulla

5. Excoriations

- Superficial excavations of epidermis: linear or punctuate, result from scratching, biting or rubbing
- Produced by self trauma; often linear pattern

6. Fissures

- Linear cleavages or cracks in skin
- Single or multiple tiny cracks to large clefts, sharply defined margins, dry or moist, straight curved or branching
- Occur when skin is thick and inelastic and subjected to sudden swelling from inflammation or trauma, especially in regions of frequent movement e.g. Ocular nasal oral or perianal mucocutaneous borders

7. Lichenification

- Thickening and hardening of skin producing exaggerated superficial skin markings
- Often results from friction e.g. Rubbing
- Often areas also hyperpigmented

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NOTES:

Chapter 2

Alopecic, Scaling and Crusting Skin Diseases: Diagnosis and Treatment Guidelines

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The major differential diagnoses producing alopecia, scaling and crusting *without* prominent pruritus include infectious dermatoses (bacterial, fungal, and parasitic), and less commonly sterile immune-mediated or miscellaneous dermatoses.

In this group of diseases pruritus will *most typically* be absent or minimal, and even when present will mostly begin only *after* lesions have developed (i.e. owners notice lesions *before* pruritus).

Fairly simple skin surface diagnostics will mostly identify the infectious differentials.

Skin biopsies will frequently be diagnostic however may not be required to confirm diagnosis for many of the infectious differentials, yet are essential for diagnosis of some diseases in this group.

A. INFECTIOUS ALOPECIC, SCALING, AND/OR CRUSTING DIFFERENTIALS

1. Dermatophilosis (“Rain Scald”, “Mud Rash”, “Mud Fever”)

Aetiology / Pathophysiology

Dermatophilosis is a common infectious skin disease in large animals caused by the bacteria *Dermatophilus congolensis.* Infection can occur from direct contact with carrier animals, or indirectly from zoospores that may remain viable in the environment for many months (e.g. in shed skin scale or crusts, and at least transiently in soil.) Skin trauma and moisture are important pathogenic factors. Disease is most common with prolonged exposure to rain, and thus is more common and severe in tropical climates, although may also occur associated with more subtle water exposure (e.g. prolonged sweating under rugs). ***Horses*** are the most classically affected animal species in Australia. Some horses are particularly susceptible to infection, and will have repeated bouts while other horses in the same conditions remain disease free. In tropical climates, dermatophilosis in herd animals can be a serious and debilitating disease, however is typically of minimal importance in Australia. ***Cattle***, ***goats***, and ***sheep*** can be affected. Disease is anecdotally reported in ***alpacas***. Close contact is often required between livestock for transmission, so minimising crowding of wet herds/flocks may help reduce disease risk. Insects including ticks, prickly vegetation, and UV damage of white skin may also predispose to disease. Rarely, dermatophilosis can be ***zoonotic****, causing pruritic or painful pustular lesions in contact areas in people.

Clinical Presentation

Early transient primary lesions are papules or pustules which rapidly progress to multiple thick crusts in the typical forms of disease. Crusts are circular, range in size from ~5mm to 5cm in diameter, and may become almost confluent yet retain individual projections creating an irregular "knobbly" appearance to crusts. In haired areas crusts classically have a base of matted hair, a concave under-surface with central hair projections ("toothbrush" appearance), and underlying purulent exudate. Lesions may be painful, and there may be concurrent oedema, pain and lameness with distal limb infections. Drier forms of crusting with a less classical appearance, and a more subtle chronic "dry" form of dermatophilosis associated with scaling rather than crusting occurs in horses. In the latter, non-adherent fine white scaling and patchy alopecia predominate.

Horses: The dorsal trunk is most commonly affected in horses ("rain scald"), and occasionally the muzzle; or distal limbs ("mud rash" or "mud fever"). Two forms are reported: the classical "wet" form, and the more subtle scaling "dry" form.

Cattle: The dorsal trunk and rump are most commonly affected, however lesions are also reasonably common in a wide range of areas including the pectoral region, axillae, groin, face, pinnae, limbs; and the perineum, and udder/teats or prepuce/scrotum.

Sheep: Two forms occur in sheep: a body form ("lumpy wool" or "dermo") that involves trunk, face and ears; and a lower leg form ("strawberry footrot"). Disease is most common in weaners and hoggets, with Merinos more susceptible than British or crossbred sheep. Thin, flat crusts predominate on the non-wool body areas. Under the fleece, early serous to greasy exudate accumulates at the base of wool fibres, producing thick exudative crusts that matt the wool which may not be readily evident without palpation. Affected sheep are more prone to flystrike.

Goats: Lesions are more common on the head (muzzle, periocular, and pinnae), dorsum, udder/scrotum, tail, or distal limbs.

Differential Diagnosis

The wet form of dermatophilosis on the dorsal trunk has a fairly classical appearance, although may be confused with dermatophytosis, exudative superficial bacterial pyoderma or early pemphigus foliaceus. In contrast, the drier forms have a number of differentials, including superficial bacterial pyoderma, pediculosis, zinc responsive dermatitis (goats, sheep, cattle), and multiple other causes of secondary seborrhoea (e.g. poor nutrition, debility, drying or irritant topical products). In goats "scabby mouth" is an important differential.

Diagnosis

Cytology usually allows confirmation of diagnosis, even with dry forms of disease. *Dermatophilus congolensis* is a gram-positive branching filamentous rod, which divides into parallel rows of zoospores in suitable conditions, forming a classical "railroad track" appearance. Organisms may be evident on direct impression smears of moist lesions, however typically require 15-minutes soaking in warm saline for zoospores to be produced. After soaking crusts or scale are gentle grasped in forceps, and impression smears prepared. Slides are air dried, and Diff quik® stained. In the author's experience, cytology is a very sensitive test for the diagnosis of dermatophilosis.

Bacterial culture may be performed, however microaerophilic conditions are ideal, and culture is therefore difficult and not reliable.

Skin biopsies for histopathology may confirm the diagnosis, or at least provide supportive evidence, typically reveal palisading crusts that may contain the filamentous bacteria.

Management

Effective treatment requires removal of prolonged exposure to moisture whenever possible, and daily topical application of antibacterial solutions: the author prefers a 2-3% chlorhexidine solution (e.g. Chlorhex C®), applied from as a spray or rinse, although additional 3% chlorhexidine or benzoyl peroxide shampooing can help with crust removal. Povidone iodine is also effective, but is inactivated faster in the presence of crusts and exudation, and may be irritating. Crusts should be disposed of carefully to avoid further environmental contamination.

Horses: Parenteral antibiotics are occasionally required in severe cases (e.g. procaine penicillin, 20 000 IU/kg intramuscularly for 3 to 5 days). Regular topical antibacterials are often protective at higher risk times in susceptible individuals, although some protection from constant rain is required. Better rug hygiene, and ensuring hosing down after exercise and drying before repeat rugging are important in the dry form of disease.

Cattle: Most cases resolve spontaneously when environmental conditions improve. Reduced wetting from sprays, or the use of regular antibacterial solutions, can be considered for chronic disease in dairy herds.

Sheep: Penicillin: high doses ‘several’ times may be necessary with drying of skin for at least 48 hours to limit fleece damage.

2. Dermatophytosis (“Ringworm”)

Aetiology / Pathophysiology

Dermatophytosis is common in ***horses*** and ***cattle*** throughout the world, and less common in ***sheep***, ***goats***, and ***pigs***. In horses it is caused most frequently by *Trichophyton equinum,* although a range of other species may be implicated, including *T. mentagrophytes, Microsporum equinum, M. canis, and M. gypseum*. In production animals it is most frequently caused by *T. verrucosum,* although *T. mentagrophytes, T. equinum,* or *Microsporum spp.* are occasionally involved. *Microsporum nanum* is the commonest implicated species in pigs. It is common in riding and racing horses, particularly from stables, with young animals more susceptible. Cases occur more commonly in autumn and winter in cooler climates, especially in confined animals and during warm moist weather in warmer climates. Transmission may be via direct contact, or indirectly via grooming equipment, tack, clippers or contaminated boxes. Some dermatophyte species are more virulent than others, although some form of skin damage is typically required for infection to establish. The incubation period may be up to 4 weeks. Dermatophytosis is a zoonosis; transmission is rare with the common *T. equinum equinum* infections, and more common with *T. equinum autotropicum* (Australia and New Zealand), or *T. verrucosum* infections. Large animal dermatophytosis is ***zoonotic****, although considerable variation occurs in virulence between fungal species and strains.

Clinical Presentation

Primary lesions are *well-demarcated* areas of alopecia (infected hair shafts weaken and readily break), papules and occasionally pustules. There is often secondary scaling, erythema, and/or crusting, and erythema, oedema, and exudation can occur with severe disease. Early lesions may resemble wheals associated with urticaria.

Pruritus is occasionally prominent, but mostly absent.

Horses: Lesions are most common in the girth, saddle, neck or facial regions (due to mild physical trauma at these sites).

Cattle, Sheep, Goats: Lesions are most common on the head (face, pinnae), neck, and rump/tail or perineum. Crusting is very prominent in cattle and sheep, and is typically thick and greyish to white in colour. Alopecia is more prominent in goats.

Pigs: Lesions may occur anywhere on the body however are most common on the head (face, pinnae) and trunk. Large annular macular areas of erythema to brownish skin discolouration are classical. Pustules may be evident at the periphery of lesions. Thick brown crusts may develop with chronicity.

Differential Diagnosis

Dermatophilosis, superficial bacterial folliculitis and less commonly pemphigus foliaceus are the main differentials. Urticaria (with multiple underlying aetiologies) may be a differential for some early lesions. Zinc-responsive dermatitis is another differential for cattle, sheep and goats, sterile eosinophilic folliculitis/furunculosis for cattle, and “scabby mouth” for goats and sheep.

Diagnosis

Diagnosis is confirmed by cytology and/or a positive dermatophyte culture in combination with consistent historical and clinical findings. Samples for both culture and cytology should be collected from the margins of active lesions, collecting both hairs and skin surface debris and keratin.

Trichograms and tape preparations (the latter easily pick up broken hairs from affected areas) may reveal fungal spores and/or hyphae (KOH preparation is not required as most animal dermatophytes cause ectothrix infections [on the outside of hairshafts]). The author finds tape preps in particular to be fairly sensitive: allows fairly quick searching at low power (4X) for broken swollen hair fragments that typically have numerous fungal spores or hyphae (evident at 40X to100X power). The absence of any fungal elements on cytology does not preclude this diagnosis.

Fungal culture samples should be sent to a commercial laboratory for fungal identification, as some specialised techniques may be required for equine dermatophyte species. Knowing the causal species aids with prognosis, identifying the most likely source of infection, and directs the importance of environmental decontamination. Fungal culture may also sometimes be negative, and occasionally falsely positive.

Histopathology will confirm dermatophytosis, and is useful when cytology and fungal culture are negative, or in atypical cases where the culture of transient skin flora is considered, although culture remains important to determine the fungal species involved. Wood’s Lamp examination will be useful in only a small group of patients, being positive only with M. equinum (and also 50% or M. canis infections).

Management

Infection is usually self-limiting, with spontaneous remission occurring in 1 to 3 months in healthy animals, however the risk of contagion and zoonosis must be considered, and treatment to hasten resolution is often indicated in horses, and may be important for valuable cattle or those destined for export. Topical treatments are often effective; the author’s preference is topical 0.2% enilconazole rinse (Imaverol®; every 5-7 days for a minimum of 4 weeks or until beyond resolution of lesions. Chlorhexidine (e.g. Pyohex®, 3%) or Povidone iodine shampoos can help with removal of crusts and surface debris prior to application of the rinse. Systemic Griseofulvin has not been clearly evaluated in the horse, and is not currently recommended for treatment. Overseas, 2% lime sulphur rinses have been used, however no veterinary product is available in Australia. Environmental decontamination is vital in eliminating infections from stables or outbreak situations, as fungal spores can remain viable for months to years. Household bleach (sodium hypochlorite 5%) is one of the most effective agents for solid surfaces, but must be used with care. Bedding, rugs, brushes and combs, and tack should be disposed of (especially with virulent infections) or thoroughly cleaned, dried, and disinfected.

3. Superficial Bacterial Infections

A number of forms of superficial bacterial infection occur in skin, and there is some confusion with nomenclature. ***Impetigo*** is a superficial pustular form most common in young animals or associated with the udder/perineum region. It is very common in ***cattle***, particularly lactating females of dairy breeds, but also reported in ***sheep*** and ***goats***, also most commonly in breeding females. ***Exudative epidermitis*** is a common acute exudative vesiculopustular form that occurs in ***pigs***. ***Superficial bacterial pyoderma*** (also referred to as bacterial folliculitis/furunculosis) refers to a variable crusting superficial disease not consistent with impetigo. There is some confusion with nomenclature: cases with folliculitis evident on histopathology will look similar to forms without, and the term *pyoderma* is therefore preferred by the author. Underlying aetiology and management are similar for all forms of superficial bacterial infections.

Aetiology / Pathophysiology

Frequently caused by coagulase positive *Staphylococcal* spp., superficial bacterial infections are all secondary skin diseases, most typically associated with relatively minor underlying problems, including skin surface trauma (e.g. ill-fitting tack and saddles, heavy riding; trauma from offspring or milking machines during suckling/lactation), stressful times (e.g. parturition), and excessive rugging +/- inadequate grooming in horses. Other less common underlying diseases in large animals include hypersensitivities, and other primary causes of skin trauma. Disease may be more frequent in spring and summer associated with higher temperatures and humidity, coat shedding, increased training schedules (horses), and increased insect populations. In pigs, trauma, inadequate nutrition, other diseases, and environmental stress (e.g. overcrowding) have all been implicated. *S. aureus* and/or *S. hyicus* are most frequently implicated in all animal species, with *S. aureus* the most prevalent except in the pig where *S. hyicus* subspecies *hyicus* dominates disease. Apparent outbreaks can occur in racing stables, and in cattle, sheep, or goat herds, possibly associated with more virulent bacterial species, however often associated with climatic conditions, or problems in coat management (e.g. irritant washes, frequent rugging, rugging immediately after exercise (sweating) and routine hygiene (shared tack and rugs). Some strains of *S. hyicus* produce exfoliative toxins producing severe disease.

Infections can progress rarely to *Staphylococcal* mastitis in cattle, mostly associated with milking trauma.

Clinical Presentation

In all animal species, primary lesions are papules, and less commonly pustules. Secondary lesions may predominate, including scaling, crusting, and alopecia: initially raised hairs over palpable papules, giving a ruffled patchy appearance to the coat, progressing to demarcated, roughly circular patches of alopecia from 2-3mm to occasionally 5-8mm or greater. Lesions may progress to nodules +/- draining tracts when furunculosis occurs. Pruritus is often unapparent.

Horses: Lesions are most common in the saddle and tack areas, or on the pasterns and heels (e.g. "greasy heal").

Cattle, Goats, Sheep: *Impetigo* lesions are most commonly seen on the udder or perineum, and may also involve adjacent areas on the medial thighs, ventral tail, and ventral abdomen. Pustules are typically visualised despite being transient, and form circular crusts after rupturing. *Superficial bacterial pyoderma* lesions ("folliculitis/furunculosis") may occur anywhere on the body, although are most frequent at trauma sites including the rump, tail, and perineum; face; and distal limbs.

Pigs: Suckling and recently weaned piglets are mainly affected. Acute, subacute, and chronic forms of disease are recognised, with the latter in weaned pigs, and the more acute forms in suckling pigs. Up to 90% of piglets can be affected, with an average mortality of 20%. In the *Acute* form, dark brown greasy exudate ("greasy pig disease") and thick brown crusts which becomes generalised; starting around periocular areas, followed by pustules on the nose, mouth, and coronet regions, before progressing. In the *Subacute* form lichenification and wrinkling of skin follows the acute lesions, and progresses to cracking of thick crusts. The *chronic* form is characterised by waxy brown crusts and erythema predominantly confined to the head, including pinnae, and is not associated with illness.

Differential Diagnosis

Dermatophilosis and dermatophytosis are the major infectious differentials, with all 3 differentials producing well-demarcated alopecic and crusting lesions. Pemphigus foliaceus will similarly produce well-demarcated lesions. Louse and mite infestations may sometimes mimic superficial bacterial infections, although alopecia tends to be patchy and poorly demarcated with these differentials.

Other differentials include viral infections; in cattle for udder lesions pseudocowpox, bovine papular stomatitis [parapox virus], and herpes mammillitis; and in sheep and goats for facial lesions “scabby mouth”. In the pig lesions are fairly characteristic however parakeratosis is one far less common and sporadic differential (nutrition-related metabolic disorder).

Diagnosis

Diagnosis is often suspected with consistent history and physical examination, however confirmation requires surface skin cytology (tape preparations most useful for dry alopecic skin; impression smears for moist skin; fine needle aspirates for nodules), revealing neutrophils with intracellular bacteria (typically cocci). Where pustules are present, gently pricking the pustule with a fine gauge needle (e.g. 23g) and then making an impression smear is helpful. Confirmation can be difficult with early cases with minimal alopecia and no pustules. Bacterial culture and sensitivity from tissue biopsies can be helpful, particularly with nodular lesions, however is often problematic with superficial infections as culture results may reflect normal flora or transient organisms rather than the pathogenic bacteria. Histopathology can be helpful to confirm or support a diagnosis, however classical change and/or bacteria will not always be evident (NB It is important not to do any surface skin preparation prior to biopsy collection, to increase the diagnostic findings).

Management

Topical antibacterials are often effective for superficial infections. The author’s preference is 2-3% chlorhexidine solution (not surgical scrub) sprayed twice daily on affected areas (leaving on for residual action) until resolving well, then gradually reduced. Twice weekly application can be preventative against further recurrences if primary problem relatively minor (e.g. repetitive trauma).Chlorhexidine or benzoyl peroxide shampoos once to twice weekly help with removal of crusts and exudation if present, and are useful to clean coats and remove surface debris, although antibacterial action is only transient. Other options include iodine solution or sprays (discolours white hairs, can cause irritation). More severe lesions, including all cases with furunculosis, may require systemic antibiotics. Ideally a minimum 3-week course is required, for which trimethoprim sulphur is the authors’ preference (15-30mg/kg bid). IM procaine penicillin twice daily is often effective initially, however difficult to continue for the entire 3-week course. It is important to search for underlying diseases or important factors for recurrent or severe cases.

4. Malassezia Dermatitis

This common secondary skin disease in small animal dermatology rarely affects large animals, although it has been recognised in ***goats***. Disease is associated with debility (poor nutrition, concurrent disease). Lesions appear similar to small animal forms, with prominent alopecia, scaling, and erythema, progressing to hyperpigmentation and lichenification. Diagnosis is confirmed by cytology (tape preparations, impression smears), and/or via histopathology. Treatment does not appear reported: topical enilconazole (Imaverol®) rinse twice weekly may be considered.

5. Demodicosis

Aetiology / Pathophysiology

Demodicosis is very rare in large animals, predominantly reported in ***horses, cattle*** and ***goats.*** It is caused by increased numbers of *Demodex* mites which are host-specific mites, found in low numbers as normal flora in all mammals. Disease is therefore *non-contagious*, and in all species (except for dogs where there is a juvenile form) is associated with immunosuppression (concurrent disease, poor nutrition, debilitation, stress, medications e.g. glucocorticoid treatment) allowing an increase in mite numbers. There is a strong genetic influence in dogs, and genetic predisposition may play a roll in other species also, impacting on breeding advice, however disease in large animals is only sporadic. Demodex mites all have a similar appearance across species; those associated with disease include *D. equi* in horses, *D. bovis* in cattle, and *D. caprae* in goats, although many mammals have a few species as resident normal flora.

Clinical Presentation

Primary lesions are papules, and also deep, firm nodules in cattle and goats (0.5-2cm diameter), typically with normal overlying skin. Secondary lesions include well-demarcated alopecia and scaling, although these may be absent in cattle and goats with the nodular form of disease, where draining tracts may occasionally develop. Pruritus is often absent.

Horses: Lesions are most common on the face and neck

Cattle: Lesions are most common on the neck, shoulders, pectoral regions, and forelegs, and less common on the dorsum, head and hind legs.

Goats: Lesions are most common on the face, neck and shoulders, but may be generalised.

Differential Diagnosis

Dermatophilosis, dermatophytosis, superficial bacterial pyoderma, and less common alopecic and scaling dermatoses are the major differentials in horses, and deep bacterial pyoderma, and other causes of nodular skin diseases must be considered in cattle and goats.

Diagnosis

Requires deep skin scrapings; mites are mostly plentiful.

Management

Demodicosis in large animals is rarely symptomatic, although treatment should include removal of immunosuppression wherever possible. Spontaneous resolution has also been reported. Ivermectin has been used successfully. *Amitraz rinse has been lethal in horses.*

6. Pediculosis (Lice)

Aetiology / Pathophysiology

Pediculosis occurs worldwide in horses and all production animal species, and is more common in cooler moist climates, during late winter and early spring. In Australia, ***sheep*** and ***goats*** are the most frequently affected host species. Animals in poor condition, kept together in large numbers, and/or not groomed regularly may have heavy burdens. Lice are host specific and are not contagious across species. Sucking (*Haematopinus*, *Linognathus*, *and Solenoptotes spp.*) and/or biting (*Bovicola* [formerly *Damalinia*] *spp.*) lice may be involved. Adult lice lay operculate eggs (“nits”) attached to the hairs. They do not live for more than a few days off their host; the life cycle normally takes 3-5 weeks, with adult lice living up to 40 days. Transmission is by direct animal contact or via fomites (e.g. grooming equipment, harnesses, bedding etc.).

Clinical Presentation

No primary lesions are usually evident, with secondary alopecia (patchy, irregular, poorly demarcated,) and scaling most typical creating dull dishevelled coats. Superficial erosions and/or crusting may be caused by rubbing. Pruritus is often recognised, ranging from mild to severe, although may be absent despite heavy burdens. In horses mild mane and tail rubbing, and flank biting are typical. Anaemia can occur in extremely heavy infestations of sucking lice. Lesion location depends on the louse species to some extent, with sucking lice predominantly affecting the ventral body, and biting lice more typical dorsally.

Horses: The head, neck and thighs are most typically affected with biting lice (*Bovicola. equi).*

Cattle: The biting louse (*B. bovis*) produces lesions most typically on the neck, withers and tail head. Sucking lice more commonly affect the head (poll, pinnae, periocular), neck, pectoral regions, axillae and groin.

Sheep: Three louse species affect Australian sheep: biting “body” lice (*B. ovis*), common on the shoulder, neck and back; and two species of sucking lice: *Linognathus pedalis* affecting feet, and *L. ovillus* affecting the face. The biting lice are the major problem, resulting in fleece damage from rubbing due to pruritus when there are heavy burdens. Sheep lice may survive on goats for a few weeks however this is rarely a practical problem.

Goats: Four louse species infect goats in Australia: 2 biting lice (*B. caprae* and *B. limbatus*); the latter affecting primarily Angoras and their crosses, and responsible for economic losses from fleece damage; 2 sucking lice (*L. stenopsis* [common; often mixed infections with *B. caprae*], and *L. africanus* [rare]). Biting lice most frequently affect the head, neck and dorsum, and sucking lice the groin. Large burdens of sucking lice have been associated with anaemia, especially in kids.

Pigs: The sucking louse, *Haematopinus suis* is common in pigs, most commonly on the ears, neck, axillae, groin, flanks.

Alpacas : Both biting and sucking species occur; similar disease to other animals.

Differential Diagnosis

Less aggressive forms of dermatophilosis, dermatophytosis, and superficial bacterial pyoderma may mimic pediculosis, as will some other mite infestations (chorioptes, psoroptes). Close inspection reveals lice in most animals, making diagnosis straightforward however they may be sparse to unapparent in some individuals.

Diagnosis

Adult lice (3-6mm long) and/or eggs (1-2mm long, attached to hairs) are typically visible to the naked eye, however microscopic evaluation is required to clearly identify and distinguish biting from sucking species. Biting species, light brown in colour, tend to distribute dorsally (back, mane, tail, neck). Sucking lice, blue-black in colour when filled with blood, tend to distribute ventrally. All in-contact animals should be assumed infected, even if lice are unapparent and skin appears normal on some individuals.

Management

Most adult lice are easily killed with topical organophosphates or synthetic pyrethroids (e.g. cypermethrin, deltamethrin, or permethrin), except in sheep where some resistance has developed. Sucking lice are also killed by injectable macrocyclic lactones (e.g. ivermectin or moxidectin (200ug/kg orally). Eggs are more resistant to all treatments; thus treating beyond the typical 3-week life cycle is important.

Treatment for goats and sheep is more effective immediately after shearing. The logistics of repeat treatments for large numbers of animals to ensure adequate duration of treatment means eradication is rarely achieved for large flocks; and regular treatments to reduce burdens are the more common goal.

For horses, and individual or small numbers of production animals, permethrin (e.g. Permoxin®) full-body rinse or spray weekly for 4-6 weeks is effective. Topical pour-on products (e.g. epiromectin, moxidectin, doramectin) are often more practical, however repeat treatment also necessary. It is also vital to treat all in-contact animals. The environment will not need extensive treatment if *all* animals are treated beyond 4 weeks, however cleaning of grooming equipment for horses is advised especially with heavy infestations.

7. Mite Infestations

a) Chorioptic mange

Aetiology / Pathophysiology

This is a common skin disease in ***horses*** and ***alpacas*** worldwide and is also well-recognised but less common in ***cattle***, ***sheep*** and ***goats***. It is caused by the surface dwelling, non-burrowing mite *Chorioptes*, with mite species possibly all variants of *Chorioptes* *bovis*, the species causing disease in cattle. However, transmission of infection from cattle or other ungulates to horses is not reported. In horses it predominantly occurs in well-feathered fetlocks e.g. Draft and Shire horses, and is more common in winter months, and with intensive housing. In cattle it is more common in stabled dairy cattle. It is ubuiquitous in alpacas in Australia, caused by *C. bovis*. Adult mites live in surface scale, laying eggs which hatch in 1-5 days; the life cycle is typically 2-3 weeks. Mite populations are usually larger, and therefore disease more prevalent in temperate climates and colder weather (i.e. winter). Transmission is by direct or indirect contact. All in-contact animals should be assumed infected, although susceptibility to severe disease is individually variable resulting in some animals in a herd being severely affected, and others appearing completely normal.

Clinical Presentation

Pruritus ranges from absent to intense, with foot-stamping and/or rubbing of lower limbs. Primary lesions include erythema and papules, although they may not be readily evident at well-haired sites, and more apparent secondary lesions often include scale and crusting. Alopecia is usually minimal. Marked lichenification and swelling can occur with chronicity.

Horses: Largely restricted to the fetlock and pastern areas in heavily feathered breeds.

Cattle: In Australia is classically a very mild disease, affecting the lower legs predominantly. In cooler climates of other countries it is more common on the rump, tail and perineum, udder or scrotum.

Sheep: Most common the udder, scrotum, head and lower legs; may impair fertility in rams.

Goats: Most common on the feet and lower legs; also occasionally on forelegs, perineum, udder/teats, scrotum and ventrum.

Alpacas: Common; may be generalised or affecting ventral body, legs, feet, and pinnae.

Differential Diagnosis

Superficial bacterial pyoderma, dermatophilosis, dermatophytosis, pediculosis, psoroptes and environmental mites, *Psorobia* (formerly *Psorergates*) *ovis* (itch mite) in sheep (very sensitive to macrocylic lactones: rare in Australia now), and zinc responsive dermatitis (cattle, sheep, goats, and alpacas).

Diagnosis

Typical history and clinical signs are suggestive; although confirmation requires superficial skin scrapings. Mites are relatively large (0.3-0.5mm long), and superficial dwellers, living in surface scale and debris. Scrapings can be difficult on heavily haired legs; hair should be clipped or parted, and ample surface crusting and scale collected. Mites are usually plentiful, but may be sparse.

Management

Chorioptes has been a very frustrating disease to manage in horses and alpacas: the dense and long hair coats/fleece likely creating the major difficulty. Sustained treatment of all in-contact animals (irrespective of clinical signs) beyond the 3-week life-cycle followed by quarantine measures and/or repeated prophylactic treatment prior to mixing with other animals (e.g. horse events) should be curative.

Injectable ivermectin and moxidectin (200ug/kg) are not reliably effective: their use may reduce infection but rarely eradicate disease. Topical pour-on products (e.g. epiromectin, moxidectin, doramectin) appear more efficacious, however it is important to part the coat or fleece and apply thoroughly to skin, and *critical* to repeat treatment weekly to fortnightly for *all* in-contact animals for 4-6 weeks. Fipronil spray (Frontline®: off-label use except in dogs, cats) has been reported efficacious in horses, and is the author's preferred treatment when practical. Treatment must be applied thoroughly to *all* lower limbs of *all* in-contact horses, and ideally continued once weekly for 4-6 weeks. Prophylactic monthly fipronil spray may be recommended for horses with previous chronic disease after complete initial treatment. Chronic infestation is common in groups of Draft and Shire horses, flaring most typically in winter and settling again over summer.

b) Psoroptic mange

Aetiology / Pathophysiology

Psoroptes spp. may induce skin disease in horses or production animals in parts of the world. They are non-host specific surface dwelling mites, feeding on scale and tissue fluids on skin and/or within ear canals. Transmission is via direct or indirect contact. The classical sheep form ("sheep scab"), caused by *Psoroptes ovis* was introduced to Australia with the first fleet, however eradicated after a long compulsory dipping program, and dose not occur in New Zealand. Pruritus tends to be very persistent in production animals, but may be minimal. In ***horses*** in Australia, *Psoroptes hippotis* has been associated with ear canal disease, and *Psoroptes equi* with tail and neck rubbing, however disease appears to be very rare now. Ear canal and pinnal disease, and less commonly generalised dermatitis are reported in ***alpacas*** in some parts of the world; if present in Australia, incidence appears very low.

Clinical Presentation

Primary lesions include erythema and papules, and more apparent secondary lesions often include scale and crusting, and there may be notable alopecia.

Horses: Ear canal infections produce head shaking, ear rubbing or scratching, head shyness. Less commonly trunkal dermatitis occurs (mainly mane and tail).

Cattle, Sheep, Goats: Exotic* Lesions most typically occur on the dorsum, especially the shoulders and rump.

Alpacas: Pinnal and ear canal disease most commonly; trunkal forms also reported.

Differential Diagnosis

Superficial bacterial pyoderma, chorioptes, pediculosis, sarcoptes (exotic to Australia); insect hypersensitivity in horses; *Psorobia* (formerly *Psorergates*) *ovis* (itch mite) in sheep (very sensitive to macrocylic lactones, so rare in Australia now)

Diagnosis

Demonstration of mites on superficial skin scrapings or from ear canal samples (swab sample mixed with paraffin oil) is diagnostic; the latter may require sedation. Mites are large (0.4-0.8mm long) and readily seen.

Management

Ivermectin is effective (200ug/kg orally once weekly to fortnightly for 4 weeks); although cleaning of ear canals, at least at initial presentation, is also important for ear canal disease. All in-contact animals will require treatment.

c) Environmental mites

A variety of environmental mites live in hay and grain, and huge population outbreaks can occur when environmental conditions are suitable. Adult or immature mites will feed on animal and human skin, producing irritation and dermatitis. Environmental mites are not host-specific, and horses and all production animal species may be affected. Pruritus is often prominent. Mites include trombiculids, forage, and poultry mites. They are often problematic to detect, as mites are often transient. Clinical signs are often similar for all mites, and typically affect multiple animals although the degree of irritation may vary between individuals.

Clinical Presentation

Pruritus is often intense. Lesions consist of primary papules (numerous to sparse), and secondary patchy alopecia, erythema, excoriations, and crusting from self-trauma. Lesions most typically occur on the head (muzzle) and legs, but may affect the neck and ventral abdomen with heavy infestations.

i) Trombiculids ("chiggers", "harvest mites")

   Trombicula spp, (harvest or chigger mites) are common in many parts of the world, including Europe and Australia, most typically affecting horses or live stock grazing pastures in late summer and autumn. The adult and nymph stages parasitise plants and invertebrate hosts; and larval stages cause disease. The complete life cycle takes from 50-70 days. Tiny orange-red mites, just visible to naked eye, may be present in the center of papules.

ii) Forage mites

   A variety of environmental mites from the Acaridae and Pediculoididae families live in straw and grain, and huge population outbreaks can occur when environmental conditions are suitable. Outbreaks sometimes occur in stables, affecting horses and humans in contact with infected straw. Lesions may occur on the dorsum of horses if stabled beneath food storage areas (e.g. hay lofts)

iii) Poultry mites

   Dermanyssus gallinae, the red or poultry mite, will occasionally feed on horses, cattle, and humans. Direct or indirect poultry or bird nest contact is required. Adult mites feed on blood, and are visible as red mites when engorged. Lesions may occur on the dorsum of horses if bird nest overhead.

Differential Diagnosis

Superficial bacterial pyoderma, dermatophilosis, dermatophytosis, pediculosis, other mites (chorioptes, psoroptes, *Psorobia* (formerly *Psorergates*) *ovis* (itch mite) in sheep (very sensitive to macrocylic lactones: rare in Australia now), and zinc responsive dermatitis (cattle, sheep, goats, and alpacas).

Diagnosis

Firm diagnosis requires demonstration of mites, which can be difficult.

Larval *Trombiculid* spp. are the smallest species (0.2-0.4mm long), and will occasionally be detected on skin scrapings however are often absent as they only feed briefly. A presumptive diagnosis is often made based on exposure to known *Trombiculid* areas at classical times of year, and typical physical findings. Infested environments are frequently well-known locally, although populations may vary considerably each season, depending on climatic conditions.

Forage mites are relatively large mites (0.3-0.6mm long), and may be detected on skin scrapings, combings, or tape preparations; or from forage samples (where they are usually plentiful).

Poultry mites are large (0.6-1mm long), red in colour, and visible to the naked eye however often easier to find in infected environments than on animals. They tend to feed at night, and return to the environment during the day.

Management

Mites are readily killed (organophosphates, pyrethrin) however successful treatment requires removal of contaminated sources: forage, bird nests, and pastures. Treatment of small infected environments can be considered using approved environmental insecticides (e.g. pyrethrin sprays, lime sulphur). In stables all infected straw should be removed, and stables sprayed before new bedding placed. Repeat contamination can be a problem. Repellent sprays (e.g. permethrin) on animals daily or prior to access to affected areas may be required.

8. Helminth Dermatoses

Larvae of a number of helminths are uncommonly associated with skin disease.

Horses: *Stronglyoides westeri*, a common small intestinal nematode of horses, and *Pelodera stonglyoides*, a free-living nematode found in damp soil and decaying organic matter, will occasionally invade percutaneously, typically under moist unhygienic conditions. Skin in contact regions is affected (lower legs, muzzle) with a pruritic dermatitis characterised by papules, alopecia, scaling crusts, and ulcers. (These diseases are covering in more detail in the "The Itchy Horse").

Cattle: *Stephanofilaria* cause ventral body dermatitis, more commonly in wet tropical areas. Buffalo flies (*Haematobia irritans*) act as intermediate hosts, infecting multiple animals. Lesions include papules, alopecia, scaling, ulcers and crusts, most commonly on the ventral chest and abdomen. Treatment involves control of buffalo flies, to which widespread synthetic pyrethroid, and possibly organophosphate resistance has developed. Backline sprays, spray races, and dips reduce buffalo fly numbers quickly and provide quick relief for cattle.

9. Viral Infections

Many are ***zoonotic****, producing vesicular and crusted lesions on people in contact regions.

Horses: **Horse Pox** is a mildly contagious viral disease reported in horses in Europe, Australia and North America. Disease is characterised by typical pox lesions, beginning with vesicles that rapidly ulcerate then crust. Lesions occur most common on the muzzle and face. Spontaneous resolution is typical within 4 weeks.

Herpes coital exanthema is a contagious venereal disease of horses, caused by equine herpes virus 3 that occurs sporadically in most parts of the world. Transmission may occur via coitus, insects, fomites, or inhalation. Initial lesions include small papules, vesicles to bullae, or pustules on the penis, prepuce, vulva or perineum; any may be pruritic. Spontaneous healing occurs over 3-5 weeks.

Cattle: **Pseudo-cowpox*** commonly causes small horse-shoe shaped vesicular and crusting lesions on the udder of cows, and may be problematic in dairy cows.

Bovine papular stomatitis* is an erythematous, macular and papular dermatosis affecting the mouth and occasionally other body areas including the udder and teats. It is caused by a parapox virus, mostly commonly affecting cattle <1 year of age. Transmission occurs via skin abrasions.

Herpes mammillitis is caused by bovine herpesvirus-2, transmitted by contact and insect vectors. Vesicular lesions, swelling and pain occur on the udder/teats, and may extend to the perineum and vulva.

Sheep & Goats: **Contagious pustular dermatitis* ("scabby mouth", contagious ecthyma, orf)** is caused by a parapox virus, which is very hardy and can survive on the ground for years. It is present in most Australian sheep properties. Disease occurs when skin surface trauma allows viral penetration, thus is associated with rough prickly pastures and feeds, and non-wooled areas of skin are primarily affected. Classical lesions are vesicles rapidly progressing to a sticky exudate and thick brown adherent crusting, most commonly on the lips and mouth commissures, and also on the udder/teats or feet (coronet and heal bulbs). Rams can be affected with a papillomatous form of disease, producing large proliferative lesions, which may be pedunculated, on the head, pinnae, or distal limbs. Goats tend to have less severe disease than sheep. A commercial vaccine is available for scabby mouth in sheep, and may be applied at lamb marking, however on most farms there is a high level of immunity from natural exposure. This virus is ***zoonotic****, and may cause typically solitary vesicular then crusted lesions on exposed human skin.

Sheep and Goat Pox* Are exotic to Australia: producing classical pox lesions in other parts of the world, with severe forms in Europe, Africa, Asia, and Middle East.

Differential Diagnosis

Lesion appearance and location is often characteristic for each disease. Most viral diseases in this group are characterised by transient vesicles progressing to erosions and ulcers that readily become crusted. Differentials mainly include diseases with prominent crusting, such as dermatophilosis or superficial bacterial pyoderma, and pemphigus foliaceus in horses and goats.

Diagnosis

Histopathology will usually confirm the diagnosis if the lesions are not classical, however electron microscopy, virus isolation, or PCR testing may be required for absolute confirmation.

Management

No specific treatment is available for any of the viral infections. Crusts and erosions will typically dry and resolve over 2-3 weeks. Raw erosions may be exposed if crusts are forcibly removed.

B. IMMUNE MEDIATED ALOPECIC, SCALING AND/OR CRUSTING DIFFERENTIALS

1. Pemphigus Foliaceus

Pemphigus foliaceus is uncommon in the ***horse***, although one of the more common immune-mediated skin diseases, and is also reported in ***goats***. It appears unreported in other production animal species, although may occur sporadically. It is associated with loss of intercellular adhesion in the superficial epidermis, although the exact antigen targeted in horses and goats has not been identified. A wide age range may be affected, although two groups are reported in horses; young foals from 2-12 months, and adult horses. The prognosis is generally better for foals. Disease may wax and wane.

Clinical Presentation

Primary lesions are vesicles to bullae, and pustules, which are very transient, so more typically secondary lesions predominate (extensive crusting, scaling and annular areas of alopecia). Lesions commonly start on the face or limbs, and often become generalised, although may remain localised to the face or coronary bands in horses. In goats disease is usually generalised, with the face and pinnae often severely affected. Pruritus may vary from mild to severe, however is typically not a major feature, with the crusting lesions more prominent. Systemic signs, including lethargy, pyrexia, and weight loss occur in 50%; and oedema of the ventral abdomen and limbs in >50%.

Differential Diagnosis

Dermatophilosis, dermatophytosis, and superficial bacterial pyoderma are the classical differentials. Demodicosis is a rare differential in horses. Zinc responsive dermatitis should also be considered in goats.

Diagnosis

Cytology samples from active lesions (e.g. impression smears from beneath crusts, aspirates from intact pustules, tape preparations from drier lesions) often reveal acantholytic cells with neutrophils, with or without bacteria. Biopsies for histopathology are essential for disease confirmation. As classical changes are transient, collection of multiple samples from a range of clinical lesions will increase the chances of clear confirmation from biopsies. Samples collected from primary lesions are more likely diagnostic (pustules, papules); however samples from crusted lesions, especially thicker crusts, will often be helpful.

Management

Treatment requires immunosuppression. Owner commitment is important as successful treatment is typically intensive until good control is achieved, and prolonged to lifelong. Minimal information is available for goats, and treatment is often not attempted, however glucocorticoids and gold salts have been used. In horses oral prednisolone is the mainstay of treatment, commonly recommended at 2-4mg/kg once daily initially for 2-3 weeks until clinical remission is achieved, then tapered slowly (e.g. 25% of the 48hr dose) every 2-3 weeks, reducing to alternate day therapy as soon as possible. Occasionally dexamethasone (0.2-0.4mg/kg sid) or triamcinolone are used initially, and may help to achieve remission in more severe or poorly responsive cases. Gold salts have been used successfully in a steroid-sparing role, and occasionally as sole therapy in foals. It is important to discuss potential side-effects with owners, including a possible increased risk of laminitis. The author recommends a concurrent management plan to reduce risk of laminitis, which is particularly important if triamcinolone is used; low energy diets, weight control, regular gentle exercise.

2. Alopecia Areata

Is an uncommon immune-mediated disease reported rarely in ***horses*** and ***cattle***, where destruction or damage to hair bulbs causes well-circumscribed areas of non-inflammatory hairloss.

Clinical Presentation

Primary lesions are small to large circular patches of well-demarcated alopecia, with exposed skin appearing normal. Leukotrichia (loss of hair pigmentation) may also occur. There is no associated pruritus. Lesions may be solitary or multiple, and are most frequent on the face, neck and trunk in both horses and cattle.

Differential Diagnosis

The presence of normal skin associated with well-demarcated alopecia is fairly characteristic. Other rare hairloss disorders including follicular dysplasia, and occasionally dermatophytosis with minimal skin changes, may appear similar.

Diagnosis

Trichograms from the periphery of active lesions will classically reveal broken “exclamation point” hair shafts, with breaks occurring at sites of weakness, which is highly suggestive of alopecia areata together with consistent history and clinical signs. Skin biopsies for histopathology may reveal lymphocytic attack of hair bulbs, however classical changes may be absent by the time of presentation.

Management

This is a cosmetic disease only, and no treatments have been clearly shown to be effective. Lesions may spontaneously resolve from 1-2 months up to 2 years. Minoxidil, a vasodilator that can stimulate hair growth in humans (Rogaine®), has been used with anecdotal success in some horses (2% solution applied twice daily). Whether this treatment has helped or spontaneous resolution occurred is currently unclear; however the treatment appears to be well-tolerated and safe.

C. MISCELLANEOUS ALOPECIC, SCALING, AND/OR CRUSTING DIFFERENTIALS

1. Irritant Contact Dermatitis

Aetiology / Pathogenesis

Contact dermatitis may be caused by an irritant (or non-immunological) response, or by a delayed hypersensitivity response (immunological reaction to a specific hapten). A contact reaction requires direct contact between the offending agent and skin; hair protects against direct contact, while moisture (e.g. sweating) enhances it. Irritant contact reactions have been reported in ***horses, cattle, sheep***, and ***goats*** to a variety of contact agents: topical products (sprays, rinses, wipes); bedding and tack; vegetation; caustics (acids, alkalis); oils, diesel fuel, turpentine; and body secretions (urine, faeces). Pruritus and/or pain are variable: pruritus is often less intense with irritant compared to allergic contact reactions.

Clinical Presentation

Lesions vary from mild (erythema, papules, oedema, scaling) to severe (vesicles, erosions, ulcers, necrosis and crusting).

The affected site depends on the irritant: most commonly affecting the head (muzzle, lips, pinnae) and extremities (distal legs); or the ventral body surfaces and tail region.

Differential Diagnosis

The variety of clinical lesions and body areas affected with irritant contact dermatitis means there are a variety of differential diagnoses: all the infectious, immune-mediated, miscellaneous and ulcerative alopecic and crusting dermatoses should be considered.

Diagnosis

History is vital to diagnosis in many cases, with the distribution of lesions an important clue. Histopathology changes are non-specific. Resolution after removal of contact, and relapse on provocative exposure confirm the diagnosis if there is any doubt.

Management

Identification and avoidance of the irritant substance will produce complete resolution of lesions.

2. Zinc-Responsive Dermatitis

Aetiology / Pathogenesis

This entity has been reported in ***cattle***, ***sheep, goats***, and ***alpacas***. It may be associated with a primary zinc deficiency, or with diets or drinking water excessive in calcium, iron, phytates, and other chelating agents. Pruritus is typically minimal. Secondary bacterial infections, or malassezia dermatitis in goats, may complicate disease.

Clinical Presentation

Initial erythema and scaling often progress to crusting and alopecia, affecting the face, pinnae, mucocutaneous junctions, pressure points, and distal limbs most characteristically. May have dull, rough, brittle hair coat. Lesions are usually symmetrical.

Differential Diagnosis

Dermatophilosis, dermatophytosis, superficial bacterial pyoderma, and mite infestations (chorioptes, environmental mites) are the most likely differentials. , Pemphigus foliaceus is a differential for disease in goats and cattle, and sterile eosinophilic folliculitis/furunculosis in cattle. Helminth dermatoses are a consideration for contact forms.

Diagnosis

Biopsies for histopathology provide supportive information. History including dietary details are important.

Management

Correction of mineral dietary imbalances, or long-term zinc supplementation if un-associated with diet: oral or injectable supplements are available, however are often difficult to administer long-term.

3. Seborrhoea

Seborrhoea is a poorly understood term that indicates a keratinisation defect, with excessive production (most commonly) or reduced desquamation of stratum corneum, producing clinical “scale” or “dandruff”, which is a non-specific finding. The vast majority of cases are secondary, due to an increased cell-turnover associated with stimulation from a wide variety of underlying primary diseases; with environmental conditions (e.g. topical products, stabled with heating, excessive rugging), allergic or parasitic diseases, and nutritional deficiencies most common. Occasional cases of primary seborrhoea occur, where there is an inherent decrease in epidermal cell turn-over time, producing increased layers of epidermal cells that accumulate as scale on the skin surface because they are produced at a faster rate than desquamation can occur. Primary seborrhoea should be present from a young age (6 months or younger).

Clinical Presentation

Scale is the predominant clinical sign; mostly as a secondary lesion, however very rarely as a primary lesion. It may be dry (seborrhoea sicca) or greasy (seborrhoea oleosa). Secondary seborrhoea tends to be regional or generalised, with the face, trunk, and/or legs often affected. Primary seborrhoea is very rare, and most commonly localised to the mane and tail in horses, although may be generalised.

Differential Diagnosis

A wide variety of diseases may be associated with secondary seborrhoea; the term is a descriptive one, and not a diagnosis. Differentials for the rare case of primary seborrhoea include ichthyosis, but also multiple causes of secondary seborrhoea (parasitic, nutritional, environmental).

Diagnosis

Requires skin biopsies to confirm a primary seborrhoea; however is most typically a secondary problem, suggested by excessive surface scaling on clinical examination. Resolution of scaling with treatment/correction of underlying disease or factors confirms a diagnosis of secondary seborrhoea.

Management

With secondary seborrhoea, specific treatment is rarely indicated, as management of the underlying disease/problem should result in resolution. For primary disease, or with the occasional more persistent secondary case, antiseborrheic shampoos can be helpful, starting with mildest emollient shampoos (e.g. oatmeal) and only progressing to degreasing shampoos (e.g. tar) with very greasy skin and poor response to initial products. Moisturising (e.g. Alpha Keri® bath oil rinse/spray or QV lotion® daily to weekly can also help, along with management of secondary bacterial infections.

4. Ichthyosis

Ichthyosis is a rare congenital group of hereditary keratinisation defects, characterised clinically by persistent excessive scaling. Severe forms are often lethal, and may be associated with other body organ defects. Disease is evident from a very young age.

5. Equine Sarcoidosis

This is a rare disease characterised by generalised seborrhoea, severe wasting, and sarcoidal granulomas in multiple body organs.

Scaling, crusting and alopecia begin on the face or limbs and progress to a generalised or multifocal exfoliative dermatitis, with the mane and tail often unaffected. Most horses become systemically ill, with inappetance, weight loss, and pyrexia. Diagnosis requires skin biopsies, which reveal nodular to diffuse sarcoidal granulomas. The prognosis is generally poor, with progressive deterioration; however some horses spontaneously resolve. Immunosuppressive doses of glucocorticoids, especially early in the disease course, can produce partial or complete response.

6. Exfoliative Eosinophilic Dermatitis

This is a rare disease of the horse characterised by severe eosinophilic infiltrate in multiple body organs; typically associated with a generalised exfoliative dermatosis, ulcerative stomatitis, diarrhoea and weight loss. The aetiology is unknown. Lesions often begin with transient vesicles and bullae progressing quickly to ulcers on the muzzle, coronets and mucocutaneous junctions; progressing to more prominent generalised scaling, crusting, and alopecia. Pruritus is variable. Diagnosis requires skin biopsies. The prognosis is frequently grave, with most horses progressively deteriorating over several months. Temporary response can be achieved with immunosuppressive doses of glucocorticoids.

7. Sterile Eosinophilic Folliculitis and Furunculosis

This entity is a rare idiopathic disorder recognised in cattle. Lesions are initial papules, which enlarge to alopecic, crusted plaques. They occur symmetrically on the head, neck and trunk most commonly. Histopathology is diagnostic.

8. Lupus Erythematosus

Systemic lupus erythematosus is very rare in the horse; characterised by variable multi-systemic signs which may include alopecia, depigmentation and scaling of skin (face, neck and trunk), lymphoedema, panniculitis, polyarthritis, thrombocytopenia, proteinuria, fever, depression and weight loss. Discoid lupus erythematosus is also rare; characterised by erythema, scaling and alopecia on the face, especially the lips, nostrils and periocular region. Diagnosis requires skin biopsies.

9. Epitheliotropic Lymphoma

This clinically non-specific form of neoplasia is very rare in the horse; most typically presenting with multifocal to generalised areas of alopecia, scaling and crusting; and sometimes nodules. Diagnosis requires biopsy for histopathology. Prognosis is poor. Little information is currently available on chemotherapeutic options; however response to treatment for this tumour in other animal species is often poor.

10. Exudative Dermatitis

A rare generalised exudative dermatitis is reported in horses, characterised by serous "oozing" exudation from extensive areas resulting in hair-matting, patchy hairloss and crusting. An underlying aetiology is rarely confirmed, although some cases are seasonally recurrent and hypersensitivity suspected. Pruritus may be present or absent, and some cases have been associated with urticaria. Histopathology reveals epidermal spongiotic vesicles, and eosinophilic, neutrophilic and mixed mononuclear perivascular dermatitis. Glucocorticoid therapy, as for hypersensitivities, can provide temporary response.

11. Anagen Defluxion ("Wool Break", "Wool Slip")

This uncommon alopecic disease is best recognised in the ***sheep***, with their almost continual anagen (growth) phase of hair follicles, and occasionally in ***cattle*** and ***horses.*** It is caused by a temporary defect in hair shaft structure, which occurs associated with various stress factors, including infectious and metabolic diseases, environmental factors (winter shearing of housed sheep), drugs (e.g. glucocorticoids, epidermal growth factor, and cyclophosphamide) and physiological factors (parturition, heavy lactation). In cattle, young calves are most commonly affected. Wool or hair loss occurs suddenly, within 7-10 days of the stressful event. Complete alopecia is evident, which may be multifocal, regional, or generalised, with normal underlying skin. Diagnosis is suggested by consistent clinical and historical findings, and examination of trichogram will reveal irregular breaks and deformity of hair shafts. No effective treatment is know, however lesions resolve spontaneously as new hair grows through.

D. ULCERATIVE AND CRUSTING DIFFERENTIALS

This group of diseases is relatively rare in the horse and production animals. Environmental causes and immune-mediated diseases are most common, although some hereditary disorders occur very rarely. They are characterised by ulceration and subsequent crusting. Pruritus will *most typically* be absent or minimal. Skin biopsies may be required for diagnosis, however care is important in sample selection: ulcerated areas are rarely useful; intact vesicles or bullae are ideal; or alternatively transitional samples including intact epidermis adjacent to areas of ulceration.

1. Photosensitisation (“Facial Eczema")

This disease involves the presence of a photodynamic agent within the skin, exposure to a sufficient amount of ultraviolet light, and absorption of ultraviolet radiation, which is greatly facilitated by lack of pigment and hair coat. It is reported sporadically in ***horses***, and sporadically or in seasonal outbreaks in ***sheep***, ***goats***, and ***cattle*** in Australia. Photosensitisation may be *Secondary* when the photodynamic agents are produced endogenously due to:

- Liver disease: phylloerythrin, a porphyrin produced by bacterial degradation of chlorophyll in GIT can increase with hepatic disease (infectious, degenerative, neoplastic, or toxic e.g. ingested rape, heliotrope, blue-green algae, sporidesmin [fungus growing on freshly dead pasture in warm, moist conditions])
- Porphyria (hereditary aberrant porphyrin synthesis)

Or photosensitisation may be *Primary* when a photodynamic agent is acquired by:

- Ingestion (e.g. plants including St. John’s Wort and Japanese millet, and occasionally lucerne, canola, and some clovers)
- Administration (e.g. drugs including tetracyclines, chlorothiazides and sulphonamides)
- Direct skin contact (e.g. some plants).

Porphyria is inherited as an autosomal recessive trait in cattle (Limousin and their crosses). Sporidesmin fungal toxicity induces liver disease and photosensitisation is most common in East Gippsland in Victoria, where large outbreaks occur.

Clinical Presentation

Early signs before skin lesions are apparent include restlessness and discomfort, with animals seeking shade, and/or head shaking or rubbing. Later signs range from mild erythema to severe ulceration.

Primary lesions with severe forms are vesicles, quickly followed by secondary swelling, erythema, ulceration, and crusting. Scarring and alopecia occur chronically.

Lesions occur primarily on non-pigmented lightly haired areas, however can extend into adjacent haired and/or pigmented skin, with the head, dorsum and udder/vulva most frequently affected. Distal extremities and muzzle will be affected for contact forms. Animals may also show signs of liver disease (jaundice, anorexia, ill-thrift) with secondary forms associated with liver disease.

Differential Diagnosis

Severe sunburn and resultant skin necrosis can appear very similar (occurs on white skin with unusual solar exposure e.g. sheep recently shorn); vasculitis; subepidermal bullous diseases.

Diagnosis

Diagnosis is based upon consistent clinical signs and historical findings. An accurate history (grazing habits, seasonality of signs, recent drug administration) is vital. Liver enzymes and function testing should always be performed.

Management

Short-term management relies on temporarily preventing exposure to sunlight, and good wound hygiene. Identification and removal of the photodynamic agent provides long-term control; removal from affected pasture is vital with ingested forms; spraying of pastures with fungicides in problem areas is an effective control measure for sporidesmin-induced disease.

In cases of chronic liver disease, or congenital porphyria prevention of solar exposure is the only option that may carry a fair prognosis, however this is often impractical.

2. Subepidermal Bullous Diseases

A range of subepidermal bullous diseases, difficult to differentiate with readily available diagnostics, are reported rarely in ***horses***, ***cattle***, and ***sheep***. Bullous pemphigoid, congenital or acquired Epidermolysis bullosa (EB), and Mucous membrane pemphigoid have all been reported. These diseases are caused by disruption of varying adhesion structures between the epidermis and dermis, resulting in clinical lesions of transient vesicles, ulceration and crusting that most frequently affect pressure areas: mucocutaneous junctions (lips, vulva, anus, eyelids), axillae, groin and the oral cavity. Diagnosis requires skin or mucosal biopsies, revealing subepidermal clefting and vesicle formation, and immunofluorescence or immunohistochemical staining to demonstrate the antigen target characterising each disease. All reported cases of Bullous pemphigoid in the horse have been severe and progressive, so the prognosis is grave; although aggressive immunosuppressive therapy can be considered in early cases. Hereditary congenital forms of EB are reported in horses, cattle and sheep.

3. Cutaneous Asthenia

Is a group of inherited, congenital diseases characterised by loose, hyperextensible and fragile skin, including Ehlers-Danlos syndrome, dermatosparaxis, and hyperelastosis cutis. It has been reported in Quarter ***horses*** and occasional other horse breeds, in some breeds of ***cattle*** or their crosses (Belgian, Charolais, Hereford, Holstein-Friesian, and Simmental), and in ***sheep*** (Australian Border Leicester-Southdown crosses, Romneys, and Finnish crossbred merino’s are amongst affected breeds. Some forms are autosomal dominant, and some recessive. In addition to regions of hyperextensible skin, there are often areas of skin tearing and ulceration, which heal with scarring, that are recognised from a young age. Diagnosis is suspected with classical historical and clinical findings, and supported by abnormalities in collagen fibre appearance and arrangement in the deep dermis on histopathology, requiring special stains or electron microscopy to clearly identify. Minimising skin trauma is the only possible management plan currently.

4. Erysipelas

This uncommon disease affecting ***pigs*** is caused by the bacteria *Erysipelothrix (insidiosa) rhusiopathiae* and most commonly affects piglets from 3months of age up to 3-year old pigs. It occurs in acute, subacute, and chronic forms, with more severe lesions, pyrexia and illness in the more acute. Typically multiple animals are infected, and lesions range from skin cyanosis (bluish, purplish discolouration) to necrosis followed by complete ulceration, characteristically in square, rectangular, or rhomboidal plaques (“diamond skin disease”). Erysipelas is a ***zoonosis****. Diagnosis is often based on classical lesion appearance, but can be confirmed by bacterial culture (organism most readily grown from heart blood, liver or spleen samples collected at post mortem; often not readily grown from skin samples), or via skin biopsy or necropsy (histopathology reveals neutrophilic vasculitis).

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NOTES:

Chapter 3

Diagnostic Approach to Nodular Dermatoses

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INTRODUCTION

The appearance of a solid skin swelling greater than 1cm, which exceeds the dimensions of a papule, can be included in the category of nodular skin disease. Many forms of skin disease may originate as macules or papules but progressively increase in size, either singly or in numbers, and so become included in this category.

Nodules can be subdivided into either inflammatory or neoplastic lesions. The inflammation may be due to injury or infection and the inflammatory infiltrate will vary from blood and tissue fluid through to neutrophils, lymphocytes, histiocytes, plasma cells and eosinophils. Visible nodules develop from this substrate as the infiltrating cells begin to aggregate to wall off the injury or the infective process. As the lesion enlarges, the dermis and subcutis become completely infiltrated by the above cells and the overlying epidermis may become atrophic, leading to erosion, ulceration and possible exudation of contents.

Most neoplasms of the skin and subcutaneous tissue originate as nodules and then usually increase by cell division. As secondary inflammatory changes occur around them they develop into typical tumours of the skin which may present as enlarged nodules, verrucous forms, or develop ulcerative changes and necrosis. Swellings also include urticarial swellings, abscesses and body swellings such as hernias and cysts. Urticaria is covered later in the chapter Abscesses are localised fluid to solid filled lesions. They are the result of inflammatory changes, usually related to trauma and/or infection and consist of dead cells, debris and local tissue components which have liquefied through proteolytic and histolytic enzymes. While usually related to infection, abscesses can be sterile.

Tumours, nodules and swellings tend to be primary disease sites and in horses are infrequent manifestations of systemic disorders. The major disease considerations in establishing a differential diagnosis are physical causes, infectious diseases, hypersensitivity reactions, sterile inflammatory diseases and neoplasia. It is often more helpful for a clinician faced with an unknown skin disease to consider diseases based on common typical presentations rather than aetiology.

Some diseases exotic to Australia are included: transportation of horses occurs world wide and some equine diseases are found in southern Asia and Indonesia and may illicitly gain entry to northern Australia.

Nodular dermatoses covered in this presentation are grouped in classifications as listed below, based on typical presentations. This categorization is to aid the clinician in considering the major relevant differentials when faced with an unknown or unfamiliar disease. It is important to remember that atypical presentations of diseases will occur, so that some diseases will present at times with lesions inconsistent with this classification. Regardless, there will often be clues from the history and/or clinical lesions to help guide the most appropriate differentials. Although the horse is the focus of this presentation, the same principles apply to nodular lesions in production animals, and where relevant, brief notes on other species are provided.

A) DERMATOSES TYPICALLY PRESENTING AS MULTIPLE PAPULES TO SMALL NODULES

This group of diseases is characterised by dermatoses typically presenting with multifocal regional to generalised papules to smaller nodules that tend to remain covered by intact skin, and may be variably haired.

1. Bacterial Folliculitis and Furunculosis

Folliculitis is an inflammation of the hair follicle with an accumulation of inflammatory cells within the follicle lumen, which can be caused by bacteria or fungi, or may be sterile. As the inflammatory process proceeds, degeneration of the hair follicle may occur, leading to rupture of follicles and subsequent loss of contents into the surrounding dermis and subcutis (furunculosis). Where multiple inflammatory sites coalesce, a carbuncle or a boil is formed. These occur in horses with saddle boils, heat rash, cheek abscess and pigeon breast. *Staphylococcal spp.* bacteria are most commonly implicated, however *Streptococci, and C.*

pseudotuberculosis may be involved. Folliculitis and furunculosis also occurs in ***cattle***.

Aetiology / Pathophysiology

Unhygienic skin conditions complicated by areas of rubbing by harness, rugs or saddle cloths cause injury and infection of hair follicles. Coagulase positive staphylococci produce endotoxins, haemolysins, leukocidins, and dermo necrotoxins and are responsible for some cases of cellulitis and/or exfoliation.

Clinical Presentation

Acute disease: rapidly developing, small, painful papules followed by the presence of oedema and exudation. There is an increasingly acutely painful response and horses may kick or bite while being examined.

More sub-acute to chronic disease: multifocal papules to small nodules, with minimal to no oedema or exudation; may be completely haired to partially alopecic; often firm on palpation and may be mildly sensitive to non-painful on palpation. Often occur in areas of repeated trauma e.g. saddle region, however may be more generalised.

Cattle: Lesions most common on the rump, tail, perineum, distal limbs, neck or face.

Differential Diagnosis

Other infectious diseases (e.g. saprophytic fungi, habronema, actinomyces, nocardia); sterile diseases (e.g. eosinophilic granuloma, amyloidosis, insect bites); or early neoplastic diseases (e.g. mastocytoma, lymphosarcoma, sarcoids).

Diagnosis

Deep tissue biopsies for histopathology to confirm diagnosis, and for bacterial culture and sensitivity testing to identify causative bacteria.

Management

Systemic antibiotics are indicated for minimum 3-4 weeks, ideally based on culture and sensitivity testing. There are limited studies evaluating typical cutaneous bacterial flora, and their antimicrobial sensitivity patterns, in horses in Australia and around the world.

Trimethoprim-sulphadiazine 13mg/kg orally every 12 hours is the most practical option for many cases; however oral enrofloxacin (poultry powder) or injectable gentamicin, penicillin, or cephalosporines are alternatives for valuable horses or severe cases where TMS-resistance is apparent.

Surgical drainage of larger lesions may be necessary, followed by systemic antibiotics and topical antimicrobials. Topical therapy, including Povidone-iodine solutions or 1-3% chlorhexidine solution may be helpful adjunctively, and may help to prevent recurrence as part of an improved skin hygiene management plan.

Prognosis

Fair: can be very slow to resolve, and may be recurrent if the underlying cause cannot be addressed. Many early cases resolve completely with appropriate prolonged antibiotic therapy.

2. Equine Eosinophilic Granuloma

One to several, firm dermal nodules occurring on the neck, withers or back. Probably one of the more common of nodular skin conditions in the horse.

Aetiology / Pathophysiology

Unknown. Previously erroneously thought associated with degenerative collagen. Multifactorial, but may be related to insect hypersensitivity. Two thirds of the cases in one study occurred in spring and summer. A role for chronic inflammation is proposed in some cases, as lesions may occur under saddles at pressure points, and at previous injection sites.

Clinical Presentation

Fully haired, hard, subcutaneous papules to nodules between 0.5-5cm diameter. Single, several or many lesions appear, most commonly on the withers and back. They are painless and non-pruritic, although may cause discomfort during riding when located under saddle regions.

Differential Diagnosis

Other infectious (e.g. bacterial folliculitis/furunculosis, bacterial pseudomycetoma, saprophytic fungi), sterile (e.g. amyloidosis, insect bite) and early neoplastic (e.g. mastocytoma, lymphosarcoma, sarcoids) diseases. Epidermoid and dermoid cysts should be considered for more solitary lesions.

Diagnosis

Deep skin biopsies for histopathology required to confirm diagnosis. Mineralisation may occur in old lesions.

Management

Using corticosteroids is the only successful treatment apart from surgical removal. Where large numbers of nodules are present, use 600-800mg oral prednisolone daily for 10-14 days, followed by 500-600mg/day for another 10-14 days; inject any remaining lesions intra or peri-lesionally with triamcinolone 3-5mg/lesion or methylprednisolone 5-10mg/lesion. Many nodules are very dense and may require the use of a pressure syringe and 25G needle, or else inject peri-lesionally. Surgical ablation should be considered where lesions remain after prolonged corticosteroid treatment, or have become calcified. Topical potent steroid preparations (e.g. mometasone [Elocon®]) have been effective early in recurrent cases. Treatment should also involve removing repetitive trauma where identified (e.g. ill-fitting saddles).

Prognosis

Recent cases show a better response than chronic cases. Calcified lesions need surgical removal.

3. Urticaria

Urticaria is a common entity in the horse, characterised by sudden onset of multiple oedematous pitting papules to nodules, and associated with a wide variety of factors. It is also reported rarely in cattle.

Aetiology / Pathophysiology

The oedema results from mast cell degranulation via immunological or non-immunological mechanisms, caused by drugs (systemic or topical e.g. antibiotics, vaccines), hypersensitivities (atopy, food reactions, insect hypersensitivity), physical factors (cold, heat, pressure), psychological factors (stress, excitement), and infections (bacterial, fungal, viral). Approximately 50% of cases in horses remain idiopathic. In cattle, a unique autoallergy to their own milk can occur. It is most common in Jerseys and Guernseys.

Clinical Presentation

The head, neck, shoulders and thorax are most commonly affected; can be regional or generalised. Multiple wheals that pit with digital pressure occur; often circular although may be irregular serpiginous lesions; range from tiny papules (1-2mm) to giant plaques (20-30cm) and may be single or coalescing. Individual wheals are transient (few hours), however new lesions may continue occurring so appear persistent. Secondary surface serum oozing and crusting may occur with severe cases, or patchy alopecia and scaling with chronic cases. Pruritus is most typically absent.

Differential Diagnosis

Lesions are usually very characteristic. Early dermatophytosis, insect bites, or erythema multiforme may occasionally appear similar.

Diagnosis

Characteristic clinical lesions that pit on digital pressure confirm urticaria. A range of further diagnostic tests and trials may be indicated to search for the underlying cause, including drug withdrawal, intradermal testing for atopy and insect hypersensitivity, and food trials, particularly with persistent or recurrent cases.

Histopathology of acute lesions is generally unrewarding, however may help confirm underlying diseases or exclude some differentials at times.

Management

Some untreated cases resolve spontaneously. Antihistamines are ideal for acute or chronic cases (e.g. chlorpheniramine 0.25-0.5mg/kg bid; diphenhydramine 1-2mg/kg bid-tid), however sedation and drug-withdrawal problems for performance can occur. Glucocorticoids may be less effective, however many horses have good response (e.g. dexamethasone 0.1mg/kg sid IM; oral prednisolone 1mg/kg sid). Side effects must be considered for long-term treatment. Adrenalin (s/c) is treatment of choice in people for severe type-1 hypersensitivity reactions, including urticaria, and should be considered in horses.

Prognosis

Good, although more guarded in recurrent cases without identifiable underlying causes, where repeated bouts can interfere with performance.

4. Papular to Nodular Parasitic Dermatoses

Apart from fly/insect bites and demodicosis, other nodular parasitic dermatoses generally occur in restricted locations around the world.

a. Fly/mosquito bites

May cause multifocal papules in multiple horses in a group, associated with large numbers of insects (flies, sandflies, mosquitos) breeding and feeding in waves. Irritation and lesions rapidly subside as insects die. It is most typically associated with obvious irritation, in suitable environmental conditions.

b. Demodicosis

This is a very uncommon condition in horses unless their immune system is compromised. A very uncommon clinical disease even though mites can be demonstrated regularly, i.e. *D. caballi* from eyelids and muzzle, and *D. equi* from the body of normal horses. Clinical disease is related to alopecia, scaling with papules and pustules. Positive skin scrapings and evidence of lowered general immunity in the horse may then involve clinical signs of Demodicosis.

Unlike in other animal species, demodicosis in ***cattle*** and ***goats*** is a nodular skin disease. It is typically asymptomatic, and mainly recognised at slaughter.

c. Hypodermiasis

This economically important disease in ***cattle*** is caused by the warble flies (*Hypoderma bovis* and *H. lineatum*) that are found in many countries in the northern hemisphere; and occasionally affects horses. Migrating larvae form nodules in the dermis, about 2cm in diameter, often with a central breathing pore. They are most commonly located over the withers. Diagnosis is made on the appearance of the lesion. The lesions can be poulticed or surgically lanced to express the warble fly. Care should be taken as killed larvae have been recorded as causing cases of anaphylaxis.

d. Parafilariasis

*Exotic to Australia

The adult filarid *Parafilaria multipapillosa,* found in Eastern Europe, lives in subcutaneous nodules in infected horses. Nodules generally develop discharging tracts and a haemorrhagic exudate that contains eggs and larvae, often visible on cytology. Lesions occur over the neck, shoulders and trunk. The disease is more prevalent in spring and summer; and cases tend to recur annually for 3-4 years before resolving.

e. Dracunculiasis

*Exotic to Australia

Adult *Dracunculus* spp. worms, found in Africa, Asia and North America, live in subcutaneous nodules in a number of animal species, including the horse. Lesions are typically solitary nodules on the limbs or trunk that often ulcerate, and release masses of larvae when in contact with water. Nodules may be surgically excised or the worms, up to 100cm long, gradually removed by winding carefully onto a stick over several days.

5. Viral Dermatoses

A number of viral dermatoses may present in this manner, including

a. Papillomatosis

A viral skin disease characterized by small warts on the nose, lips, around eyes, inside of the ear and very occasionally, on the neck and legs in horses. Papillomatosis is common in cattle, and sporadically causes very severe disease.

Aetiology / Pathophysiology

Horses: A DNA papovavirus causes two distinct clinical forms of papillomatosis: viral papillomatosis and aural papilloma. Restricted in the main to young horses 9-36 months, and occasionally seen affecting aged horses (over 25 years). Lesions are divided into 2 main forms (mucosal and aural), and tend to increase in number rather than size.

Cattle: There are at least 5 types of papilloma virus producing a variety of clinical lesions including typical fibropapillomas, small "rice grain" warts, and low, flat "atypical" warts

Clinical Presentation

In horses the mucosal form produces small, cauliflower-like, warty growths on muzzle and lips most commonly. Aural plaques consist of small grey to white plaques on the internal surface of the pinnae (uncommon in Australia).

Differential Diagnosis

Sarcoid, squamous cell carcinoma, equine molluscum contagiosum.

Diagnosis

In Australia clinical appearance, age of horse, and size and number of warts are usually highly suggestive In UK massive numbers of small sarcoids can present a similar appearance

Biopsy for histopathology can be performed to confirm: important in atypical cases.

Management

In most young horses warts drop off after 3-4 months There is a gradual change in colour of the warts from grey to a pinkish tinge when this occurs the warts are shed soon afterwards. There often little grounds to treat horses unless the warts are causing interference to cornea or bleeding around the eyes,nose or mouth There may be little regression in the aged horse and again the appearance in old > 25yr old horses has been regarded as a loss of immunity gained as a young horse, and aural lesions may sometimes not resolve in young horses. In cattle, the typical fibropapillomas forms often spontaneously resolve also within 1-12 months, however the "atypical" and "rice grain" forms rarely spontaneously resolve.

Surgical removal or cryotherapy of warts from around the eyes and commissures of the mouth may be needed. Topical interferon-alpha (Roferon-A®) has been useful for hastening resolution of problem lesions in dogs and humans, and has been anecdotally helpful in horses. Topical imiquimod (Aldara®) may also be considered: interferon and imiquimod are immune-stimulants with antiviral properties.

Prognosis

Excellent.

b. Equine Molluscum Contagiosum (Uasin Gishu disease)

*Exotic to Australia

A mild contagious cutaneous infection caused by unclassified pox viruses. Affected horses typically have hundreds of papules, predominantly on the chest, shoulders, neck and limbs, although may be limited to localised areas: penis, prepuce, scrotum, mammary glands, thighs, axillae and muzzle.

Papules may be haired initially, although become alopecic, and are typically covered with a powdery white scale. Some develop a central pore with caseous plug, typical of this virus. Diagnosis is suggested by typical clinical appearance. Biopsy for histopathology will confirm. Lesions may spontaneously regress, although often persist for months to years. No successful treatment has been reported.

c. Equine Viral Arteritis (EVA)

*Exotic to Australia

A viral disease associated with abortion, infertility and skin disease. Some strains are relatively avirulent and infection may go unnoticed and undiagnosed. It is contagious via coitus and inhalation, and occurs in many parts of the world, characterised by oedema of the distal limbs, and occasional papular to urticarial lesions on the back.

d. Horse Pox

This rare mildly contagious viral disease in horses, reported in Europe, Australia and North America, is caused by a pox virus. Disease is characterised by typical pox lesions, beginning with vesicles that rapidly ulcerate, and then progressively crust. Lesions occur most common on the muzzle, face and genital organs. Spontaneous resolution is typical within 4 weeks.

e. Herpes Coital Exanthema

This contagious venereal disease of horses, caused by equine herpes virus 3, occurs sporadically in most parts of the world. Transmission may occur via coitus, insects, fomites, or inhalation. Initial lesions include small papules, vesicles to bullae, or pustules on the penis, prepuce, vulva or perineum; any may be pruritic. Spontaneous healing occurs over 3-5 weeks. Similar to other herpes diseases where resistance is lowered as in mares at parturition the disease there can be recrudescence and so infection of a naïve stallion

f. Other Viral Diseases

A number of other viral diseases in the horse will occasionally have cutaneous signs. **Vesicular stomatitis** (*Exotic to Australia), restricted to regions in North and South America, is associated with systemic illness, and causes vesicles and ulcers in the oral cavity, and occasionally on the prepuce, udder, and coronets. **Equine papular dermatitis** is reported in North America, Australia and Africa, and caused by a pox-virus. Annular to papular lesions are most common on the trunk and scrotum. Affected horses remain systemically well, and lesions resolve spontaneously.

6. Miscellaneous Uncommon Papular to Nodular Dermatoses

a. Erythema Multiforme

This poorly understood disease is uncommon in the horse. It is typically acute and self-limiting, and caused by individual keratinocyte cell death associated with multiple triggers, including drugs, infections, and neoplasia. Lesions are often bilaterally symmetrical on the trunk and legs, with no associated pain or pruritus, and include macules, papules, urticarial plaques, and classical “target lesions” with a peripheral raised erythemic rim and central resolving area. Biopsy for histopathology is diagnostic. Spontaneous resolution is typical. However occasional horse show recurring signs often years apart

b. Equine Unilateral Papular Dermatosis

Most frequently seen in yearlings and 2 year-old horses. Papules and nodules appear in multiple numbers, usually forming a loose group in a circular arrangement.

Aetiology / Pathophysiology

Unknown. Most commonly reported in Quarter horses but has been seen in TB and STB horses.

Clinical Presentation

Numerous, even-sized, firm, round, well-circumscribed nodules, with no alopecia, ulceration, pruritus, or pain. Fresh nodules may occur in almost concentric rings around the original lesions.

Differential Diagnosis

Dermatophytosis (before hair is lost), insect bites, insect hypersensitivity, onchocerciasis

Diagnosis

Based on consistent history, clinical appearance and the absence of any known micro-organisms.

Skin biopsy for histopathology will help exclude other causes.

Management

Oral prednisolone 1.1m/kg 24 hourly may help in some cases.

Prognosis

Good. Regression occurs over a period of time.

c. Amyloidosis

This rare disease is associated with amyloid deposition in the respiratory mucosa or skin. Cutaneous lesions include papules, nodules or plaques, most commonly occurring on the head, neck or shoulders. It usually occurs in older horses.

Biopsy for histopathology is diagnostic.

d. Equine Calcinosis Circumscripta

Characterized by firm nodules, usually over the lateral stifle area .less commonly on carpus and tarsus

Aetiology / Pathophysiology

Developmental/congenital nodule in young horses

Clinical Presentation

A nodular mass, with an aggregation of calcified granules in a white crumbly base; located most commonly over the lateral stifle area and less commonly over other joints such as the carpus and tarsus.

Differential Diagnosis

Fibrosis of acquired bursa, foreign body, calcified haematoma

Diagnosis

History, radiography, ultrasound exam; and biopsy for histopathology to confirm.

Management

Complete meticulous surgical removal-- can be difficult to immobilise and prevent fluid accumulation post surgery.

Prognosis

Good.

e. Cysts

i. Dentigerous Cysts

Hard swellings which occur between the base of the ear and eye (temporal region) and arise from tooth germ tissue. Occasionally they are also found on the cranial vault or maxillary sinus and contain enamel-forming tissue; may contain one or more tooth. Drainage may occur out near the ear through the skin.

ii. Dermoid Cysts

Single or multiple, firm to fluctuant, smooth, round cysts, with usually normal overlying haired skin. Most commonly occur along the dorsal midline of the thorax and back, and while there is no breed predilection, an Australian survey indicated they occur more frequently in Thoroughbred yearlings.

Aetiology / Pathophysiology

Congenital, developmental and possibly hereditary lesions are thought to be due to embryonal displacement of ectoderm into the subcutis.

Clinical Presentation

Single to multiple nodules covered with skin 10-15mm diameter are usually found on the dorsal midline from withers to rump. These contain soft cheese-like grey material and coiled hairs. Young horses are usually affected between birth and 18 months.

Differential Diagnosis

Epidermoid cysts, dentigerous cysts, hypodermiasis.

Diagnosis

Location and clinical picture. Excisional biopsy shows a cyst wall lined with stratified squamous epithelium containing adnexal structures.

Management

Total surgical ablation of cyst wall and contents.

Prognosis

Very good following surgery.

iii. Epidermoid Cysts

Usually solitary cysts, 7-30mm diameter, occurring on the head and legs. They are freely movable, well circumscribed, firm to fluctuant on palpation, and contain a yellow to grey mucoid fluid. Atheroma is a type of epidermoid cyst that occurs as a hemispherical 10-50mm structure located in the false nostril.

Aetiology / Pathophysiology

The cause is unknown. They are classified according to differentiation of epithelial lining.

Clinical Presentation

Large nodules, usually singular, and containing only a mucoid fluid and no hairs.

Differential Diagnosis

Dentigerous, false nostril, dermoid and conchal cysts, hypodermiasis.

Diagnosis

Histopathology: epithelial lining which shows maturation and keratinisation typical of the epidermis BUT contains no adnexal structures.

Management

Surgical removal.

Prognosis

Excellent as long as all cystic lining material is removed.

7. Neoplastic Papular to Nodular Dermatoses

Certain skin tumours are very common in horses. When confronted with a lump or bump, in or under the skin, if you are able to eliminate trauma and haematoma formation, your next step is confirmation of a diagnosis. Following careful history taking and a full evaluation of the tumour, a biopsy, or in the case of a small tumour, a total excisional biopsy (surgical removal) should be undertaken.

Biopsy for histopathology to confirm the diagnosis is advised for all tumours, and will be a major determinant of how the case is managed in the future.

a. Basal Cell Carcinoma

A rare, slow growing, well-demarcated tumour, often with an ulcerated surface, located in the neck, pectoral regions and trunk.

b. Fibroma and Fibrosarcoma

Lesions are often single, may be firm or soft, well-circumscribed, dermal or subcutaneous nodules which may ulcerate or develop into a flattened verrucous type lesion. Fibroma is the most common neoplasm encountered in the horse's frog.

Aetiology / Pathophysiology

An uncommon tumour of the horse arising from dermal or subcutaneous fibroblasts; usually occurs in older horses.

Clinical Presentation

Dermal or subcutaneous nodules which may ulcerate. Verrucous to cauliflower-like growth on the head, legs neck and flanks

Differential Diagnosis

Sarcoids, lymphoma, other tumours.

Management

Total surgical excision required. Cryotherapy is only partly successful. Radiation is more successful.

Prognosis

Good for Fibroma, guarded for Fibrosarcoma.

c. Haemangioma and Haemangiosarcoma

Uncommon tumours of the vascular system.

Aetiology / Pathophysiology

These tumours are benign or malignant neoplasms arising from the endothelial cells of blood vessels.

Clinical Presentation

The presence of numerous tortuous and enlarged blood vessels, occurring on the elbow, groin, thorax and distal limbs; may ulcerate and bleed very easily.

Differential Diagnosis

Lymphoedema, other tumours.

Management

Complete surgical ablation, usually best performed under general anaesthetic.

Prognosis

Fair for benign but a very poor outcome for malignant cases.

d. Malignant Fibrous Histiocytoma

A rare giant cell tumour.

Clinical Presentation

Lesions are solitary, firm and poorly circumscribed. They frequently occur on the neck and proximal limbs, are locally invasive and slow to metastasize.

Management

Radical surgical excision.

Prognosis

Poor: recurrence is common due to their locally invasive nature

e. Leiomyosarcoma

Very rare tumours arise from the smooth muscle cells of erector pili muscles or cutaneous blood vessels.

Clinical Presentation

An ulcerative tumour exhibiting moderately rapid growth and often malodour that is clinically similar to squamous cell carcinoma.

Management

Total surgical removal.

f. Lipoma and Liposarcoma

Uncommon to rare tumours formed from subcutaneous lipoid tissue, usually seen in older to aged horses; also occurs in the abdominal cavity causing strangulation of bowel and colic.

Management

Wide surgical excision

Prognosis

Very guarded for the malignant form.

g. Lymphangioma

A rare benign tumour of lymphatic vessels.

h. Lymphoma (Non-epitheliotropic and Epitheliotropic)

Any tumour involving the lymphoid tissue. There are many variations.

Clinical Presentation

A depressed, ulcerated lesion with subcutaneous spread, slight discharge and some crust formation.

Management

Wide surgical removal.

Prognosis

Guarded: size-dependant

i. Lymphosarcoma

This tumour is infrequently seen as a skin only neoplasm in the horse. It occurs more as generalized, thoracic or abdominal forms with cutaneous lesions.

j. Mast Cell Tumours or Equine Mastocytosis

Usually presents as a single cutaneous nodule characterised by a focal aggregation of mast cells, eosinophils, collagen aggregation and occasionally mineralisation. Multiple lesions can occur and these appear to be less responsive to treatment.

Clinical Presentation

Male horses are more commonly affected than female. Occurs as single papule to nodules, 2-20mm in diameter. The surface may be normal, hairless or ulcerated.

Differential diagnosis

Equine eosinophilic granuloma, Amyloidosis

Diagnosis

Impression smears or aspirates may show large numbers of mast cells; however histopathology is required to confirm diagnosis.

Management

Surgical ablation. Oral Cimetidine has been used as a treatment; results are equivocal

Prognosis

Guarded

k. Melanocytoma and Melanoma

The nomenclature for melanotic tumours is complex. Either term describes the black pigment tumour occurring more commonly in grey and white coated horses.

Aetiology / Pathophysiology

Equivocal.

Melanocytomas are uncommon benign neoplasms arising from melanocytes. Melanomas are common malignant neoplasms arising from malignant proliferation of melanocytes.

Clinical Presentation

Some families of grey horses have a higher incidence of these neoplasms. They manifest as small hard tumours in the subcutis, slowly increasing in size. Commonly found around the anus, vulva, tail and prepuce and less commonly, the parotid region, eyelids and lips. They occur sporadically anywhere on body, usually as a multiple type tumour except in ‘other’ coloured horses when it may occur as a single tumour; may erode through the skin and ooze black exudate. Clinically melanocytoma are only ‘depots’ of melanin pigment, are non-invasive and cause disruption by bulk.

Melanomas (melanosarcoma) are rapidly invasive and often respond poorly to surgery.

Diagnosis

The most common tumour found in grey horses; clinical appraisal including location; biopsy or complete removal and histopathology.

Management

Individual tumours on other than grey horses can be surgically removed. Slightly more caution in prognosis should be given with grey horses, even though the majority of ‘black’ lumps are benign. Wide surgical excision, cryotherapy, biologic response modifiers and chemotherapy are the modalities which give the most successful response.

Small or single tumours (<3cm diameter) are usually more successfully treated by wide surgical excision or cryotherapy. Surgical excision alone can in some horses, stimulate rapid tumour regrowth caused by stimulation to abnormal melanoblasts in the proximity to the surgical site.

Other horses are reported to develop large sheets of melanotic tumour tissue from merging or coalescence of numerous smaller tumours, e.g. around tail, anus and vulva. These are more suitable for cryonecrosis with a double freeze thaw cycle, especially for those tumours which are inaccessible to total surgery, e.g. anal sphincter area. The tumour is debulked and the remaining inaccessible area is treated by cryotherapy. This rarely ‘cures’ the problem but it allows a further useful life span for the treated horse.

The role of histamine (H2) and the growth of tumours may be related to activation of T suppressor cells. The drug **Cimetidine** is a potent H2 blocker and it has been used in the treatment of melanoma. Its successful use may be related to active growth but where growth has been minimal or even static the response can be very poor. The normal response is of a slowing of growth. If after 3 months medication there is either minimal or no cessation of growth, then no benefit is gained from further treatment. Dosage is 2.5mg/kg three times daily or less satisfactory is the total daily dose of 7.5mg/kg given once or twice daily. A response is indicated by a slow decline down to 50% of pre-treatment size and occurs during the first six weeks of treatment. The progression of the tumours may be halted for months to years following cessation of treatment.

The use of chemotherapy in melanoma has been restricted to Cisplatin. Tumours >3cm should be debulked and **Cisplatin** injected into the base of the tumour at the rate of 1mg/cubic cm of tissue every second week for 4 treatments. The drug is an irritant and the use of 22-25 gauge needles is advisable to stop back leakage following injection. The drug is injected as the needle is withdrawn in order to fill the needle track. Injection sites should be spaced 5-8mm apart as diffusion of the drug is limited. Post-treatment therapy to minimize post-injection swelling includes the use of penicillin or potentiated sulphur drugs, plus an anti-inflammatory such as phenylbutazone. This treatment has been used on stallions and pregnant brood mares without side ill effects.

Re-occurrence in unsuccessful cases occurs in 7-8 months following therapy; repeat treatment may be used following the same procedure used in the initial treatment. Cisplatin has to be freshly prepared and when reconstituted is only stable at room temperature for approximately 15 hours

Prognosis

Guarded.

l. Neurofibroma (Schwannoma)

A tumour of peripheral nerve tissue May occur anywhere associated with nerve sheath tissue but predominantly in the upper and lower eyelids.

Aetiology / Pathophysiology

Involves dermal or subcutaneous Schwann cells. The cause of the neoplastic change is unknown.

Clinical presentation

Small (1-10mm), hard, subcutaneous nodules; may be multiple. Growth of the nodules causes erosion through the overlying skin, allowing development into a fibroblastic type lesion. **Rarely show hair loss** until ulceration occurs.

Differential diagnosis

Sarcoid.

Diagnosis

Surgical removal and histopathology. Depending on the pathologist, may be diagnosed as Neurofibroma or Sarcoid. It is clinically a distinct lesion and has a different clinical appearance from sarcoids located around eyelids.

Management

Complete surgical removal is required; tumours reoccur in a different site in the eyelid in approximately 25-50% of all operated cases.

Injection of tumour with BCG cell line 1-4 injections, 28 days apart has shown some success.

Prognosis

Guarded. Persistent but multiple surgeries will prolong useful life.

m. Sebaceous Gland Tumours

These are quite rare tumours arising from sebaceous gland cells. They occur in adult to aged horses, are solitary and vary from nodules to alopecic lobulated growths, and may occur anywhere. Treatment involves surgical excision or cryotherapy.

n. Sweat Gland Tumour

An uncommon tumour of the apocrine sweat glands, occurring in older horses, and most commonly around the ears and vulva. They present as single firm to cystic dermal nodules which are usually benign and resemble sarcoids. Complete surgical ablation is the treatment of choice. The prognosis can be good but is related to size, rate of growth and accessibility.

B) DERMATOSES TYPICALLY PRESENTING AS NODULAR TO DIFFUSELY SWOLLEN AND DISCHARGING LESIONS

1. Abscess

Aggregation of leucocytes (pus) and tissue debris related to skin and subcutis which may be infected or sterile. ***Horses***, ***sheep***, ***goats***, and ***pigs*** are commonly affected.

Aetiology / Pathophysiology

Infected abscesses can be caused by a variety of organisms but those more commonly involved include:

Horses: *Streptococcus equi, Corynebacterium pseudotuberculosis* and *Clostridium* spp.; often associated with intramuscular injections or wounds, but can be disseminated through the lymphatic system. Ectoparasites were incriminated in one outbreak of *C. pseudotuberculosis*.

Cattle: *Arcanobacterium pyogenes* most commonly. Lesions are most common on stifles and hocks, although can occur anywhere.

Sheep, goats: *Corynebacterium pseudotuberculosis* is the predominant bacterial species. Lesions can occur anywhere on the body, although more commonly on the face, neck, or sternum.

Pigs: *Arcanobacterium pyogenes, β-haemolytic streptococci, Staphylococcus aureus, S. hyicus, Bacteroides spp.*; most commonly on shoulder, neck, flank, pinnae, and tail, following wound contamination (fighting, surgery, ectoparasites).

Clinical Presentation

Usually a subcutaneous swelling that may fluctuate. Acute abscesses are attached to the skin and may be hot and painful. Chronic abscesses may be walled off and may or may not be attached to the skin. Clostridial abscesses show gas formation, acute swelling and severe pain.

Differential Diagnosis

Haematoma, cyst, acute eosinophilic granuloma, hernia.

Diagnosis

Bacterial culture is required to confirm the bacterial species involved: ideally tissue samples collected with sterile technique; or fine needle aspiration from areas of cellulitis or intact nodules. Normal flora and surface contaminants are often easily cultured, especially from draining tracts and surface exudates, even when completely incidental to the disease. Results of bacterial culture should always be supported by cytology findings, ideally using fine needle aspirates from intact nodules or cellulitic regions.

Cytology also provides a more immediate indication of the likely species involved based on gram staining and appearance of organisms.

Ultrasound examination may allow aspiration from fluid pockets.

Management

Use surgical drainage and appropriate antibiotics.

Clostridia spp: aeration of affected tissues by extensive surgical incision is important.

Prognosis

Very good if full drainage is established; poor if pockets of infection remain.

2. Cheek Abscess

Acute abscess formation at or around the lateral commissures of the mouth.

Aetiology / Pathophysiology

Caused by penetration of the buccal mucosa by grass, barley or oat awns, or lacerations by cheek or wolf teeth on buccal mucosa, followed by infection.

Clinical Presentation

Acute painful swelling of 'bit' area or adjacent cheek area; small area of exudation over pointing abscess, hair loss (alopecia).

Differential Diagnosis

Bit injury in the mouth; cuts inside the commissures; foreign bodies.

Diagnosis

Cuts or wounds inside the mouth adjacent to the abscess; the presence of a 'boil' on cheek or mouth commissures, evidence of a badly fitting mouth bit.

Ultrasound.

Management

Hot and cold fomentations. Incise when the abscess points. Early use of antibiotics should be avoided.

3. Physical Injuries

Injuries to the skin and underlying tissues may result in superficial trauma to the epidermis right through to joint, bone and muscle injury. This is manifest as related to skin conditions by alteration to the normal contour of the skin and may lead to misdiagnosis between cellulitis, haematoma, bursitis and hernias.

Bursitis

A change in size of a bursa overlying a joint or tendon caused by acute or chronic trauma, leading to over secretion of the fluid within, being either normal secretion, inflammatory fluids or even pus. Chronic trauma over bony prominences may result in acquired bursa such as capped elbow or hock

Bruising is extravasation of blood into the dermis and epidermis without severe dislocation of the external epidermal layer.

Haematoma is rupture of blood vessels in subcutaneous tissues leading to extravasation of blood into the interstitial tissue.

Cellulitis is extravasation of cellular fluid into tissue space; may or may not be infected.

4. Bacterial Granulomas

A pyogranulomatous lesion associated with skin injury.

Aetiology / Pathophysiology

Lacerations and puncture of the skin followed by infection, typically with *Staphylococcal* spp. bacteria (bacterial pseudomycetoma; previously called botriomycosis), or other bacteria including *Actinobacillus*, *Nocardia* and *Actinomyces*, which invade subcutaneous tissues. The will often slowly progresses to multiple miliary interlinking abscesses discharging through multiple sinuses. Mostly occur on lower limbs or muzzle, at sites of previous trauma; occasionally on scrotum after castration. In ***cattle*** "lumpy jaw" is associated with *Actinomyces* spp., and "wooden tongue" and facial or neck nodules with *Actinobacillus* spp. Bacterial granulomas occur sporadically in individual animals. *Actinomyces* spp. also cause nodular granulomas in ***pigs***, most commonly on the udder or ventral abdomen.

Clinical Presentation

Alopecia, slowly healing wound, induration of edges, and chronic purulent discharge from one or more sinuses with rosette formation of granulation tissue around sinuses completes the clinical picture.

May also present as solitary firm nodules, often developing draining tracts and ulceration, with white to yellow granules in discharge.

Cattle "Lumpy jaw" characteristically presents as firm immobile swelling that develop draining tracts with honey-coloured discharge which contains hard, yellow-white sand-like granules ("sulfur granules"). Lesions are most common on the mandible and maxilla. Actinobacillus typically produces whitish to green discharge, with grayish to brownish white "sulfur granules".

Differential Diagnosis

Other infectious (e.g. saprophytic fungi, pythium, habronema), sterile (e.g. foreign body, eosinophilic granuloma, amyloidosis, insect bites) and early neoplastic (e.g. mastocytoma, lymphosarcoma, sarcoids).

Diagnosis

History of type of injury. Cytology reveals pyogranulomatous inflammation, often with numerous multinucleated giant cells.

Biopsy for histopathology. Bacterial culture (tissue sample) will indicate causative organism.

Management

Surgical excision or debridement. Sodium iodide solution intravenously 66mg/kg body weight every 7 days until iodism occurs. Systemic antibiotics (e.g. oral trimethoprim sulfur) will produce complete resolution if drainage established, however may be required for 4-6 weeks or longer. Surgical excision is curative for solitary lesions. Lesions are often asymptomatic, and may also gradually resolve without treatment.

Prognosis

Guarded without adequate debridement and drainage, as re-infection can occur following surgery with a return of a similar clinical entity.

5. Mycobacterial Granulomas

Ubiquitous, free-living opportunistic mycobacteria rarely cause granulomas in horses or ***cattle***. Infection usually occurs after trauma or injection. Single to multiple nodules, or chronic subcutaneous abscesses and fistulae occur. The distal limb is a more commonly affected site. Diagnosis is confirmed with histopathology and/or mycobacterial culture (opportunistic mycobacteria are rapid growers, relatively easily cultured in the laboratory). Treatment principles are as for small animals: prognosis is guarded unless lesions are excisable.

6. Fungal Granulomas

This group of diseases typically occur as chronic slowly growing fungal infections of subcutaneous tissues, which may cause generalised swelling, sinus and fistula formation, and tissue granules which may be coloured black, white or yellow. Most affected horses show pruritus.

a. Eumycotic Mycetoma

Aetiology / Pathophysiology

Eumycotic mycetomas are caused by saprophytic often soil-borne fungi that typically gain entry via wound contamination. The commonest reported fungus is *Pseudoallescheria boydii* (white-grain)*;* however other fungal species can be involved (e.g. *Curvularia geniculata* (black-grain))

Clinical Presentation

Ulcerating nodules occur on limbs, head or ventral abdomen with chronic discharge from granulating sores and pruritus. Early nodules are firm and asymptomatic.

Differential Diagnosis

Other infectious (e.g. phaeohyphomycosis, actinomyces, nocardia, bacterial pseudomycetoma), sterile (e.g. eosinophilic granuloma, amyloidosis, insect bites), and neoplastic diseases.

Diagnosis

Biopsy for histopathology. Fungal culture necessary to identify fungal species.

Management

Some respond well to surgical removal and use of systemic iodides. Some prove difficult and require repeat treatments. Adjunctive antifungal therapy can be considered, especially where complete surgical excision is not possible, and should ideally be based on sensitivity testing. Ketoconazole, itraconazole, and amphotericin B are other options.

Prognosis

Prolonged treatment may be unsuccessful.

b. Phaeohyphomycosis

A chronic subcutaneous and potentially systemic fungal disease, often beginning as small multiple subcutaneous papules to nodules. Causative fungi are pigmented (dematiaceous). *Drechslera (Bipolaris) spicifera* and *Alternaria alternata* have been isolated.

Aetiology / Pathophysiology

Caused by various soil saprophytic fungi contaminating wounds.

Clinical Presentation

Small, black, denuded plaques containing papules and pustules. Small, multiple, fibrotic, subcutaneous nodules can occur on the neck, body and legs.

Differential Diagnosis

Other infectious (e.g. phaeohyphomycosis, actinomyces, nocardia, bacterial pseudomycetoma), sterile (e.g. eosinophilic granuloma, foreign, insect bites), and neoplastic diseases.

Diagnosis

Biopsy and culture on Sabouraud's agar.

Management

Surgical excision ideal wherever possible. Adjunctive or sole medical treatment options reported include systemic iodide treatment, Amphotericin B, ketoconazole, topical application of etisazole in DMSO: insufficient data for firm recommendation

Prognosis

Guarded unless complete surgical resection possible.

7. Panniculitis

Multiple subcutaneous nodules may affect the trunk, neck and proximal limbs. Nodules may or may not be painful to palpate.

A rare, multifactorial, inflammatory condition of the subcutaneous fat of horses. The cause of the disease is obscure. Vitamin E deficiency has been suspected in some cases.

C) DERMATOSES TYPICALLY PRESENTING AS PROMINENT NODULES WITH ULCERATION AND EXUDATION

1. Exuberant Granulation Tissue ("Proud Flesh")

This entity is very common in horses, especially associated with non-healing wounds on the distal limbs.

Aetiology / Pathophysiology

The inherent slow epithelialisation of lower leg skin, frequent movement, and in some cases wound contamination, irritation, or infection with bacteria, fungi, or nematodes (e.g. habronema) may all be involved in pathogenesis.

Clinical Presentation

Ulcerated nodules typically on lower limbs that progressively granulate and fail to epithelialise.

Differential Diagnosis

Habronemiasis, squamous cell carcinoma, pythiosis, zygomycetes, fibroblastic sarcoid, bacterial pseudomycetoma.

Diagnosis

Often suggested by the typical clinical signs at a previous wound site, however biopsy is necessary to exclude other potential differentials or complicating factors (e.g. concurrent habronemiasis)

Management

Treatment involves surgical excision of excessive granulation tissue, good wound hygiene, treatment of any secondary bacterial infections, and avoidance of any topical irritants (including simple products like povidone iodine). Bandaging in some cases may help to limit further granulation tissue formation. Cleaning with saline or dilute chlorhexidine (0.05-0.1%) solution, and application of silver sulfadiazine (Silvazene®) topical cream twice daily after surgical removal of excessive tissue can be successful, with or without light bandaging. Every attempt should be made to prevent any inhibition of or disruption to epithelialisation; making careful bandaging technique important, using non-adherent dressings.

2. Squamous Cell Carcinoma (SCC)

An invasive tumour of the skin, sinuses, gastrointestinal and reproductive tracts, that is common in ***horses***, ***cattle***, and ***sheep*** with non-pigmented sparsely haired skin.

Aetiology / Pathophysiology

A malignant tumour arising from keratinocytes, frequently involved with skin exposed to actinic (solar) radiation caused by increasing altitude, decreased skin pigmentation and sparse hair coat. The irritant nature of equine smegma is implicated in male genital SCC. Irritation due to these factors may be a trigger for accelerated neoplastic growth.

Clinical Presentation

A small granulating sore which may be depressed below skin level, eroding into normal tissue. There is often malodour even with early lesions. Located on the penis and prepuce, they may vary from cauliflower-type to erosive. On the vulva and anus they are often slow-growing. On the eye and eyelid they often start as white raised plaques at the edge of eyelid or corneal/scleral junction, and may progress rapidly as their appearance changes to granulomatous and ulcerated lesions. Around the nose and mouth they appear as a depressed ulcer which progresses to a granulomatous and malodorous growth/erosion.

Differential Diagnosis

Sarcoids, other tumours, papillomas, exuberant granulation tissue, habronemiasis, pythiosis, zygomycosis.

Diagnosis

Total excisional biopsy for histopathological examination.

Management

Wide surgical excision, cryotherapy, irradiation and chemotherapy are used with varying degrees of success related to the invasiveness and accessibility of the tumour. Radioactive implants with Gold-198, Cobalt-90 and Iridium-192 offer increased chances of survival. Early tumours are more successfully surgically removed, with complete remission in most cases. Where wide excision can be performed, results are equally good, e.g. amputation of the tail, enucleation of the eye, complete removal of the eyelids, or amputation of the penis. Less successful are invasive tumours of long-standing on the eyelids, prepuce, mouth, and to a lesser extent, the vulva in the mare.

Prognosis

Guarded.

3. Habronemiasis

Infestation of wounds with the larval forms of the stomach nematodes *Habronema muscae, Drachia megastoma* and *H. majus* commonly cause ulcerative cutaneous granulomas in horses. Larvae are capable of penetrating intact skin. Recurrence of infection can occur on a yearly basis. It is associated with increased fly population, poor manure collection or disposal, and moist patches of long grass. A predilection has been shown for light-coloured horses

Aetiology / Pathophysiology

Caused by the combined presence of *Habronema* spp. stomach worms, house and/or stable flies and poor hygiene. It is most prevalent in summer and autumn. Cutaneous habronemiasis is part hypersensitivity reaction and part seasonal, with spontaneous regression in the winter months as larvae do not over winter in the tissues. It is a sporadic disease with only individual horses in a herd affected on a recurring annual basis.

Clinical Presentation

Rapidly granulating sores at the medial canthus, prepuce and urethra or elsewhere the occurrence of rapid growth of granulating wounds with fail to heal. Cheesy sulphur like granules in sores are found especially in the medial canthus. Some sores show a stringy serosanguinous exudate. Multiple areas can be affected. Urethral process infection can lead to bleeding during covering by stallions and may reduce fertility and produce blood-stained urine. Rubbing of eyes, very mild pruritus and biting at lesions also occurs

Differential Diagnosis

Exuberant granulation tissue, squamous cell carcinoma, pythiosis, zygomycetes, fibroblastic sarcoid, bacterial pseudomycetoma.

Diagnosis

Biopsy and histopathology show the presence of yellow granules in wounds with a nodular to diffuse dermatitis. Cheesy ‘kunkers’ are often present Scrapings and smears from lesions may give false positive results, e.g. finding *habronema* spp. larvae in sarcoids, in *Pythium* spp. lesions and squamous cell carcinoma lesions as a multiple clinical problem.

Haemorrhage from enlarged urethral process.

Management

Oral ivermectin paste is very efficient but occasionally a second dose is required 3-4 weeks after the initial dose, followed by regular dosing.

Surgical removal of some lesions of the medial canthus, 3rd eyelid or urethral process is possible; follow up treatment of eye lesions by oral medication may also require a local application of cortisone drops, plus 50% mixture of ivermectin and artificial tears solution. Recently it has been shown that parental corticosteroids (Dexamethasone 0.04mg/kg orally q24h or Prednisolone 1mg/kg orally q24h continued and tapered off over 20-30 days) have given a better response in cases with larger mass involvement. Average recovery time was approximately 23 days.

Control of fly breeding grounds with slashing long grass, prompt and proper manure and soiled bedding disposal and control of house and stable flies is essential.

Prognosis

Good but all aspects of control as well as treatment must be followed.

4. Pythiosis (formerly Phycomycosis)

Chronic subcutaneous, ulcerative and granulomatous, subtropical and tropical skin disease caused by fungus *Pythium insidiosum* affecting horses of all breeds, ages and sexes. Other names include Bursatee, Florida horse leech, Swamp cancer.

Aetiology / Pathophysiology

It is caused by *Pythium* spp. free-living aquatic organisms which are not true fungi, typically found only in tropical climates**.** Horses become infected by standing for long periods in stagnant water containing rotting organic material at high ambient temperatures i.e. 30º to 40º C. Damaged skin assists the entry of the organisms.

Clinical Presentation

Rapidly progressive and invasive nodular lesions are typical. Pruritus with biting and kicking at affected area is followed by subsequent ulceration of skin or wound. Sticky, serosanguinous, stringy discharge either mats hairs or hangs from body wall and/or legs in thick mucopurulent strands. Large 1-2 mm aggregations of organisms (kunkers) are found buried in the fibrous tracts. Lymphadenopathy occurs in chronic cases, and involvement of joint and tendons with sinus formation is a serious complication.

Differential Diagnosis

Sarcoid and other neoplasms, habronemiasis, fungal granuloma, bacterial pseudomycetoma, exuberant granulation tissue, zygomycosis.

Diagnosis

A quick diagnosis is vital due to the rapidly progressive nature of this disease. Pythiosis occurs where horses have access to water-logged pasture or lagoon creeks and exhibit characteristic clinical signs. Early lesions should be biopsied with fresh samples taken for culture and histopathology. Culture immediately on selective media such as Campy blood agar or on Sabouraud's dextrose agar. If time for arrival at the laboratory is 1 to 3 days, samples are better transported on ice packs and then cultured on non-selective blood agar.

Cytology is very important to hasten diagnosis: *Pythium spp.* may be found in direct smears or aspirates, especially from necrotic tissue (“kunkers”) as broad septate branching or non-branching hyphae, although organisms may be sparse. Ready differentiation from zygomycetes is not possible, however may not be important as treatment recommendations are the same.

PCR testing and immunohistochemical staining on formalin-fixed biopsies are available in USA for early disease confirmation, however are not readily available in Australia.

Early diagnosis and prompt surgical excision/debridement is essential for limit rapid progression of lesions in some cases.

Management

There are no reported cases of spontaneous remission. Surgical excision under general anaesthesia is the most common and successful treatment, particularly in chronic cases. 10% tincture iodine is packed into the surgical area and left in situ for 2-3 days, and pressure bandages are applied where possible. When granulation commences the wound can be left unbandaged. Repeat surgery is commonly necessary, especially when the lesions occur around tendons and joints. Sodium iodide 7mg/kg body weight is given intravenously as a 3.5% solution in normal sodium chloride solution and repeated in 7 days.

This is a useful adjunct to surgery and aids in the reduction of some ventral abdominal wall growths of excessive size. A phenolised vaccine has been successful in the treatment of early lesions. Successful treatment depends on the age of the horse, general physical condition, previous treatment, age/size/site of the lesion and whether there is bony involvement. Young fresh lesions of 2 weeks duration respond very well to immunotherapy alone, but response is poor if lesions are older than 2 months. Infection in the bone is usually fatal.

Prognosis

Good for body wall lesions, but guarded for lesions involving joints and tendons.

5. Zygomycosis

Zygomycetes, include a variety of ubiquitous fungal saprophytes found in soil and decaying vegetation. *Basidiobolus* *haptosporus* has been associated with large ulcerative granulomas on the chest, abdomen, head and neck similar to pythiosis with several important clinical differences. *Conidiobolus coronatus* has been associated with ulcerated nodules on the external nares and in the nasal passages with intermittent serosanguinous nasal discharge.

Aetiology / Pathophysiology

Characteristically this disease occurs in a much drier dusty environment than pythiosis. Skin injury allows entry of this soil saprophyte into the horse's body. Single lesions are common.

Clinical Presentation

As for Pythiosis, but growths are more shallow, confined to the neck and abdomen, with no isolations on legs. 'Kunkers' are small to non-existent and pruritus is moderate to severe.

Differential Diagnosis

Pythiosis, eumycotic mycetoma, exuberant granulation tissue, habronemiasis, and neoplasia including fibroblastic sarcoids.

Diagnosis

As for pythiosis, although in drier conditions. 'Kunkers' are smaller and few in number. Fungal hyphae are found in foci of necrosis on biopsy samples. Biopsy punch samples should be cultured directly onto Sabouraud's dextrose agar.

Management

Surgery is curative if all affected tissue is removed. Sodium iodide 7mg/kg body weight is given intravenously as a 3.5% solution in normal sodium chloride solution and repeated in 7 days. No vaccine is available.

Prognosis

Guarded to good.

6. Sporotrichosis

A chronic sporadic skin and subcutaneous infection caused by *Sporotrichum schenchii*.

Aetiology / Pathophysiology

Organisms occur in soil or organic debris and cause infection, usually by introduction through small skin wounds.

Clinical Presentation

Hard, subcutaneous, 1-5cm diameter nodules, associated with ‘corded’ hardened lymphatics, ulceration, creamy pus discharge and encrustation.

Differential Diagnosis

Ulcerative lymphangitis, mycetoma; and exotic diseases: histoplasmosis, glanders

Diagnosis

Nodules on lymphatic channels; culture on Sabouraud's agar slopes, gram stain exudate, biopsy not usually diagnostically helpful.

Management

Systemic and oral iodides have previously been reported as the treatment of choice for Sporotrichosis, using a 20% solution of sodium iodide slowly IV for 2-5 days, followed by oral administration at a dose rate of 20-40mg/kg/day. Side effects are common, and the newer more expensive antifungals may be safer and efficacious, although only limited information on their use in the horse is reported.

Prognosis

Guarded? May be better with new antifungals.

7. Ulcerative Lymphangitis

A mildly contagious disease in horses characterised by lymphangitis of the lower limbs. Also occurs in ***cattle***. Most commonly associated with *Corynebacterium pseudotuberculosis,* and occasionally *Rodococcus*. *equi* or *Streptococcus* spp.

Aetiology / Pathophysiology

A bacterial infection with stasis of affected lymphatics related to poor hygiene, management and insect transmission.

Clinical Presentation

There is a sudden onset of moderate to severe oedema of the lower limb. Swelling may extend to the elbow or stifle and is most common in the hind legs. Usually only one leg is affected. Serum exudate of the lower portion may occur with cording of the lymphatics of the upper leg. Ulceration and discharge of creamy, greenish pus occurs very occasionally. The leg is painful but reaction time is slow due to bulky limb oedema. Recurrence of oedema is common.

Cattle Lesions are most typical unilaterally on the distal leg; although sometimes affect the shoulders, neck, or flank. Firm nodules progress to abscesses that develop draining tracts. Cording of lymphatics also occurs.

Differential Diagnosis

Sporotrichosis, eumycotic mycetoma, cryptococcosis, mycobacterial granulomas, and exotic diseases: glanders, histoplasmosis.

Diagnosis

Clinical appearance; culture exudate; possible positive culture of Corynebacterium pseudotuberculosis, Rhodococcus equi. Strep spp. or Staph.spp

Management

Depending on the culture results, treat with appropriate antibiotics plus intravenous medication with sodium iodide 66mg/kg body weight every 7 days until iodism occurs. Chronic lymphatic nodules can be removed with elastic ligatures around the base of the swelling.

Prognosis

Guarded, as long treatment can be required.

8. Cryptococcosis

Cryptococcal spp. are ubiquitous in the environment, however infection is very rare in the horse. *Cryptococcus neoformans var neoformans*, associated with pigeon roosts and droppings, is the most common species causing infection in USA and Europe. *Cryptococcus neoformans var gattii*, associated with certain eucalypt species, is more prevalent in Australia, Asia, Africa, South America and Southern California. The most common presentations in the horse include rhinitis, nasal granulomas, and meningitis. Nodular dermal and subcutaneous masses occur rarely.

9. Exotic Nodular Systemic Diseases

a. Glanders (Farcy)

A contagious disease of horses and ***cattle*** due to aerobic bacteria *Burkholderia (Pseudomonas) mallei* that is usually fatal. It may be acute or chronic and has respiratory tract and skin forms. It has occurred in Eastern Europe, Asia and North Africa. This disease is ***zoonotic*** and can be FATAL TO HUMANS. Extreme care should be used in sampling suspect cases. This infection is transmitted from skin and nasal discharges by close contact between horses and fomites, and by ingestion of contaminated feed and water.

Clinical Presentation

It begins as subcutaneous nodules anywhere on the body, but particularly around the inside of the hocks. There is rapid ulceration of the skin leading to discharge of a honey-like secretion associated with corded lymphatics, lymphangitis and regional lymphadenopathy.

Differential Diagnosis

Ulcerative lymphangitis, histoplasmosis, sporotrichosis, mycobacterial granulomas.

Diagnosis

May be confirmed by mallein test, various serological tests (CF test, IFA, ELISA)

Culture yields gram-negative facultative anaerobic rods.

Histopathology is confirmatory, *however if submitting samples remember to tag all specimens with warning of extreme risk of handling* without proper PPP conduct in place.

b. Coccidioidomycosis

Coccidioides immitis has been commonly reported as a generally chronic, debilitating, highly infectious fungal disease in south-west USA, with spores from soil dust generally being inhaled into the respiratory tract. Very occasionally cases manifest as a skin condition.

c. Histoplasmosis (Epizootic lymphangitis)

A rare, chronic, contagious disease characterized by suppurative lymphangitis, caused by the fungus *Histoplasma farciminosum.* Occurs on the hind legs but has been reported on the neck, lips and areas where harness abrasions occur.

d. Besnoitiosis

A protozoal disease caused by ingestion of feed contaminated with cat faeces, by bites from blood-sucking insects, and parenteral injection of blood from acute cases. Cases in horses and donkeys have been reported in South Africa. ***Cattle*** are also affected in Africa, Asia, Southern Europe and South America.

e. Lumpy Skin Disease

A rare chronic viral infectious disease of ***cattle***, caused by a capripoxvirus transmitted via insect vectors. Initial signs of illness are followed by development of firm papules and nodules, initially appearing like erect tufts of hair.

10. Lymphoedema

The prepucial area may be the primary location due to a lymphatic system disorder, as seen with nodules and cording of lymphatics at this site. Swelling occurs usually unilateral of the prepuce. It may be secondary due to injury, infection or neoplasia.

Aetiology / Pathophysiology

The obstruction of lymphatic drainage due to congenital, traumatic, inflammatory or neoplastic occlusion.

Clinical Presentation

Nodules and enlarged lymphatics involving the prepuce. In primary cases it is painless but rarely fluctuates with little pitting on pressure. Secondary cases usually have other conditions involved and may be painful, pitting on pressure.

Differential Diagnosis

Haemangioma, lymphangioma, tumours, injury, post castration swelling, schirrous cord.

Diagnosis

Altered lymphatic tissue with drainage problems may be hypoplastic with the absence of lymphatic drainage, to be hyperplastic with dilation of lymphatics up to 3-4mm diameter.

Management

Surgical in some cases. Poor healing is common.

Prognosis

Guarded.

SUPPLEMENTARY READING

Scott DW, Miller WH. *Equine Dermatology* W.B.Saunders Co, Philadelphia 2003

Knottenbelt DC. *Pascoe's Principles & Practice of Equine Dermatology* 2nd Ed. W.B. Saunders Co, Philadelphia 2009

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NOTES:

Chapter 4

Equine Sarcoid: Diagnosis and Treatment Guidelines

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INTRODUCTION

The sarcoid is a locally aggressive fibroblastic tumour which is probably the most common cutaneous tumour found in horses. It is most prevalent in horses aged between 1-6 years (Torrentegui & Reid 1994; Pascoe & Knottenbelt 1999; Knottenbelt 2009). The lesions are frequently not life threatening but they can severely limit the use of the horse and reduce its sale prospects. Regardless, euthanasia is not uncommon due to the prolonged nature of treatment, likelihood of recrudescence of the problem and cost.

Population and family studies have shown an association between sarcoid susceptibility and MHC class II alleles (Lazary et al 1985, 1994). Early research indicated there were no mutations of the somatic tumour suppressor p53 gene in either horses or donkeys associated with the development of sarcoids. More recently somatic p53 gene mutations have been found to be associated with the development of some sarcoid tumours in donkeys (Nasir et al 1999).

The role of a virus, in particular bovine papillomavirus (BPV), has been proposed but is still uncertain. Viral antigen has been detected in most sarcoids tested (Nasir & Campo, 2008). BPV-DNA was detected in 88% and 91% of the successful swabs and scrapings from sarcoids respectively. The overall diagnostic sensitivity of the technique was significantly lower compared to the clinical diagnosis of sarcoids and is unsuitable for occult sarcoids. However, the detection of BPV-DNA in all samples obtained from sarcoids with an ulcerated surface opens new perspectives for the detection of sarcoid involvement in wounds or recurrence after sarcoid removal (Martens et al 2001). In a further study BPV DNA was detected in essentially all sarcoids examined (96/98), and was also detected in normal skin samples from the horses with sarcoids suggesting the possibility of a latent viral phase. Viral latency may be one explanation of the high rate of recurrence following surgical removal. All tissues from healthy horses with non sarcoid neoplasms or papilloma were negative to BVP DNA (Carr et al 2001).

Lesions occur in locations which are prone to injury and some have a history of previous skin wounds. There is also strong presumptive evidence that sarcoids can be transmitted by biting and domestic flies which feed on sarcoid tissue and then browse on other horses with open sores, wounds or tumours. The introduction of a horse with fibroblastic sarcoids can result in the appearance of sarcoids in other previously uninfected horses on a farm within 6-8 months.

The distribution of lesions varies with type of sarcoid and geographical location. The para-genital region was most frequently and the limbs least frequently affected in the UK. In Queensland, Australia the majority of lesions occur on the head, neck and limbs and very rarely in the para-genital region (Pascoe & Summers 1981).

A recent study of sarcoid cases in the UK showed single and small numbers of sarcoids (2-8 sarcoids per horse) were uncommon, whereas 10 to several thousand are more common. The majority of lesions seen in UK horses are occult or verrucous, with a total of six major types described (Knottenbelt et al 1995). The body distribution of the six types shows great variation, with a preponderance of fibroblastic tumours occurring in the para-genital area. In Australia almost all leg sarcoids are the fibroblastic type.

Sarcoids have a high capacity to invade the dermis and sub cutis, although true metastatic dissemination does not appear to occur. Sarcoids can occur in fresh healing wounds in previously normal horses, or re-occur at the same site following apparent complete surgical removal with total wound healing only to erupt in the former incision line healing.

A. CLINICAL PRESENTATIONS

1. Verrucous (Warty) Type

These tend to be slow-growing and not very aggressive until injured in some fashion, e.g. biopsy, rubbing the lesion, poor surgical removal. They present as wart-like growths on and above the skin surface that may be sessile or pedunculated.

They are often slow growing. Trauma to their surface may convert them to a fibroblastic reaction (Pascoe 1990).

Differential Diagnosis

Papillomatosis, chronic blistering, hyperkeratosis from chronic insect hypersensitivity, equine sarcoidosis, squamous cell carcinoma.

Diagnosis

Biopsy: preferably total wide excision followed by cryotherapy

2. Fibroblastic Type

A more aggressive tumour, particularly when located on the lower limbs and coronet. These begin as small fibrous nodules that progress laterally by local invasion. Erosion or injury leads to excessive granulation tissue growth. They rarely, if every, metastasize. Difficulty lies in the determination of normal and infected granulation tissue regrowth after tumour removal.

Differential Diagnosis

Exuberant granulation tissue, habronemiasis, bacterial pseudomycetoma, pythiosis, and other neoplasia (neurofibroma/neurofibrosarcoma, fibrosarcoma, squamous cell carcinoma, sweat gland tumours).

Diagnosis

Biopsy should include normal skin as well as tumour.

3. Mixed Verrucous and Fibroblastic type

This form contains both verrucous and fibroblastic elements that probably form as a progression from a verrucous type. It is progressively more aggressive as lesions change from verrucous to fibroblastic type.

Differential Diagnosis

The presence of more than one form of sarcoid is almost self-diagnostic.

4. Occult Type

This type consists of hairless areas which contain one or more small cutaneous nodules. Lesions are often roughly circular, and are very slow growing until injured. There are often one or more hard shot-like nodules in the skin (2-5mm diameter). Occult lesions may progress to warty verrucous growth or if injured, develop into fibroblastic lesions. They are commonly located around the mouth, eyes, neck or trunk.

Differential Diagnosis

Dermatophytosis, blisters, burns.

Diagnosis

Clinical picture often strongly suggestive. Remember biopsy may convert lesion into active fibroblastic sarcoid.

5. Nodular Type

This form occurs as subcutaneous nodules, which become more aggressive fibroblastic type tumours when they erode the overlying skin. Nodules are subcutaneous and spherical, and 5-20mm in diameter. They most frequently occur in the groin or eyelid areas. The overlying skin may become thin over larger nodules, and where ulceration occurs, lesions quickly develop into fibroblastic sarcoids.

Differential Diagnosis

Fibroma, neurofibroma, equine eosinophilic granuloma, melanoma, collagen necrosis (axillae - rare), dermoid cysts.

Diagnosis

Biopsy: total excision if possible with wide margins.

6. Malevolent Type (Knottenbelt DC Et Al 1995)

This form is a recent variation of sarcoids showing increased malignancy with a suggestion of metastasis adjacent to the initial site. These are still relatively rare in Australia. This form of sarcoid is very invasive, infiltrating lymphatics and lymph nodes, and metastasizing. This form may follow surgical interference to sarcoids in the jaw and elbow regions.

Differential Diagnosis

Squamous cell carcinoma, subcutaneous mycosis, ulcerative lymphangitis, and exotic diseases: glanders, histoplasmosis.

Diagnosis

Consistent clinical change to an original sarcoid is suggestive, along with invasiveness of regrowth.

Re-affirmation of diagnosis of sarcoid from new invasive tissue.

B. GENERAL MANAGEMENT CONSIDERATIONS

Due to the uncertain outcome in 100% of cases, the horse owner should be very aware of the seriousness of the problems which can arise from this disease. Treatment should involve a full discussion of treatment options, the likelihood of successful treatment, and at worst, the likelihood of prolonged or repeated treatment. It is important for owners to understand that, while the condition is contained, it may not fully resolve; and they need to be aware of the likely costs.

Assessment should be made on the following grounds:

1. The value of the animal - actual or sentimental.
2. Previous treatment and history, i.e. likelihood of chronic granulation tissue from old wire cuts or refractory granulation.
3. The cost of each avenue of treatment and the likelihood of a successful outcome to that type of treatment, i.e. repeated single local medication may eventually be much more expensive than surgical removal, radiation therapy or cryosurgery.
4. If at all possible, the results of biopsy should be known before the final prognosis is given.
5. Likelihood of further spread of the condition if treatment is:
    i. not undertaken

   ii. delayed
   iii. not correct

6. The possibility of a contagious nature of the sarcoid and the further transmission to other horses in the group.

C. OVERVIEW OF MODALITIES FOR TREATMENT OF SARCOIDS

1. Ligatures

Elastrator rings, lycra, or even heavy elastic bands can be used. Application can easily be made, even on fractious horses, using a twitch or tranquillizer. This works best on single sarcoids where loose skin on body or neck is available to allow proper placement of ligature.

2. Local Medication

Moderately successful on single small sarcoids:

- use of podophyllin 50% applied daily for > 30 days.
- 10% arsenic trioxide in aqueous solution for 5 days. Causes heavy scab formation which may be difficult to remove.
- 5-fluorouracil applied under a bandage (Roberts 1970)
- 5% imiquimod cream (Aldara®) (Nogueira et al 2006)

3. Vaccination or Stimulation of Immune System (A Little Bit of History)

Bovine wart vaccine has been used and found to be valueless. Pox vaccines used into the actual sarcoid lesion were also unsuccessful. Autogenous vaccines have been manufactured but results have not been good: recovery in fewer than 25% of animals treated (Wheat 1964; Page & Tiffany 1967). In 1977 the use of BCG vaccine was reported. Lesions were injected with BCG vaccine, 1ml at 7-10 day intervals, and a good response claimed for this type of treatment (Wyman et al 1977). A similar type treatment was made using a non-living wall preparation from BCG vaccine which was injected at intervals of 2-4 weeks. Anaphylaxis had been reported following the use of the living BCG vaccine due to proteins produced from the metabolized vaccine bacteria causing the production of antibodies which react when further treatment is given. This danger was overcome by the use of a BCG cell wall vaccine preparation which was as effective as the living BCG vaccine, but did not have the adverse side effects of producing anaphylaxis (Hepler & Leuker 1980).The reported use of such a vaccine (CSL Equoid (Australia)) for the intradermal treatment of sarcoid gave favourable results with 1-2 injections 14-21 days apart in 80% of the cases treated (Vaneslow et al 1988). However, production problems with this vaccine led to its permanent withdrawal from the market in 1993.

4. Surgical Treatment

Surgical excision: removal of sarcoid, under local or general anaesthetic, plus at least 15-20mm ring of normal**.**

Disadvantages: 50% may return; as wounds heal the sarcoid may spread to other areas on the horse; removal of large areas of normal skin precludes closure and slows healing time; inability to remove sufficient quantity of skin from leg lesions increases risk of relapse.

CO2 Laser: Complete ablation for small sarcoids is very successful; however large tumours can be less well ablated and may recur.

5. Electrocautery

Where single small masses are involved ordinary cautery is satisfactory, but re-occurrence can be expected. With large electrocautery units, both cutting and fulguration are available and should be used: remove tumour by cutting current then treat area, particularly the skin edges, with fulguration to desiccate tissue.

6. Cryosurgery

Useful for many sarcoids. Complications are under or over treatment, and injury to surrounding blood vessels, nerves, bone and tendon.

The success or otherwise of cryotherapy rests in proper observation of correct technique (Fretz & Barbour 1987). The following summary assists in understanding the modality and its side effects.

Principles

1. Select adequate 'heat' sink (best is liquid N2)
2. Freeze tissues rapidly to below -20^{o}C
3. Allow slow thaw to +36oC
4. Repeat cycle 2-3 times
5. Restrict circulation to area using tourniquet
6. Protect surrounding tissue with Polystyrene
7. Hair follicles are destroyed by double cycle
8. Vitiligo occurs with a single freeze thaw cycle; scars with double cycle
9. Bone becomes devitalized if included in freeze/thaw cycles; regeneration may take 2 years
10. Deep infiltrative tumours are seldom satisfactorily treated by cryosurgery
11. Eliminate bulk by surgical trimming before freezing

Technique

1. Use of thermocouple
2. Use of 2 cycle freeze and thaw
3. Freeze adequately
4. Protect normal tissue if using liquid spray
5. Assess patient's temperament and use the correct restraint
6. Give Tetanus antitoxin or toxoid booster
7. Give full explanation of the process and after-care to the owner
8. Do not fail to tell the owner about white hair formation

7. Radiation Therapy

Can either be a large distant irradiating source (Teletherapy) which restricts the use to a limited number of large facilities; or Brachytherapy treatment with implants or isotopes to the tumour which is more practical for equine treatments (Blackwood & Dobson 1994; Theon 1998; Knottenbelt & Kelly 2000; Henson & Dobson 2004). Squamous cell carcinoma, sarcoids, soft tissue sarcomas (fibrosarcoma, haemangiosarcoma and neurofibromas), cutaneous lymphomas and melanoma are suitable for successful treatment.

Advantages: Radiation gives less disfigurement, better therapeutic success and is good as a follow-up to failed surgery, cryosurgery or immunotherapy. Best results come with debulking surgery under general anaesthesia: previous debulking leads to residual activity of dividing tumour cells which are most susceptible to radiation and to lowered isotope cost due to smaller treatment area.

Disadvantages: Radiation requires the presence of a specialist radiologist or radio physicist, special secure areas for use of hospitalised horses, training of personnel to use care around treated horses, and increased costs due to isotopes, general anaesthetic and longer hospitalisation in specialised accommodation.

Isotopes - Strontium 90 (Owen & Barnett 1983; Fraunfelder et al 1982a), **Radon 222** (Fraunfelder et al 1982b), **Iodine 128, Caesium 137 and Gold 198** (Wyn Jones 1979,1983) and **Iridium 192** (Turrel et al 1985) have all been used. In practical terms, those commonly used are **Iridium 192** and **Gold 198** which are both gamma emitters. **Strontium 90**, a beta particle emitter has a limited penetration of 3mm, so its use is restricted to those tumours following very careful debulking or to clean-up surface cells in conjunction with implants. When applied to the target area following post surgical ablation of the tumour, Strontium 90 in an applicator has been successfully used for some sarcoids and ocular SCC.

8. Photodynamic Therapy

The therapeutic potential of the photodynamic compound, hypericin, in the treatment of equine sarcoids has been evaluated. **In vitro** cytotoxicity of three equine cell lines to phototoxic effect was comparable to that on different highly sensitive human cell lines and significantly influenced by the energy density used, although independent of the cell type. **In vivo** anti-tumoural action of photodynamic therapy using hypericin was used experimentally on three equine sarcoids and a donkey. Two 0.3% hypericin solutions were used: one in polyethylene glycol (PEG400)/H2O) or one in DMSO/H2O. Intratumoural injections were performed every 5 days under short acting GA. Mean dosage of hypericin was 0.7mg/cm^3 tumoural tissue. Tumours were illuminated over 30 min each day with a light delivery by a KL 1500 cold light source at 1 cm distance from the surface (results in an energy density of 72 J/cm2). However, this is only for a total of 25 days. 81% reduction in tumour volume was obtained at the end of therapy and 2 months later, a 90% reduction was observed. Further experimental work should be performed, but these results suggest that photodynamic therapy using hypericin has a potential for the non-invasive treatment of equine sarcoids (Martens 2000).

9. Radio Frequency Hyperthermia

This modality has been used in equine sarcoid and squamous cell carcinoma and is most successful in small tumours. Reports of treatments indicate repeat treatments are common and the method is not gained wide acceptance.

10. Chemotherapy

Many and varied compounds of inorganic tissue poisons such as arsenic, mercury and antimony, and their combinations have been used to treat sarcoids. More recently podophyllin, methotrexate, 5-fluorouracil, cisplatin and mitomycin C have been used. All require some form of repeat treatment medication, many on a daily basis for as long as 30 days. Our results are similar to those of the Liverpool Veterinary School, UK using AW-3-LUDES, with an 80% recovery rate with emphasis on initial treatment success as being a peculiarity of the drug combination (Knottenbelt & Walker 1994). Repeat treatment and treatment of previously treated unresolved lesions is likely to be less successful but still more likely than other compounds and treatments commonly used. Persistence and client compliance are important for the likelihood of higher success rates.

11. Electro Chemotherapy

Enhances the effectiveness of chemotherapeutic agents all treatments were given under short General anaesthesia. An intra tumoural drug, Cisplatin in oil, is injected into the lesion. After 5 mins two electrodes are placed over the tumour using a conductive paste and short, intensive electrical pulses (8 pulses 0.1ms at 1-Hz frequency with 1.3 kV voltages) are applied to increase the permeability of the tumour cell membrane to achieve higher cell concentrates of the injected drug. It works most satisfactorily on small tumours (<5cm). With several successive treatments at 2 week intervals, larger >10cm tumours were found to be best treated after de bulking and with multiple electro treatments simply by overlapping and shifting the electrodes. Eradication so far has been successful in all treated horses in fewer than four treatments (Tamzali et al 2003).

D. PROGNOSIS

Varies from good to poor depending on the location, number and type of lesions, and their response to initial treatment. Good client understanding is important for final resolution.

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Chapter 5

The Itchy Horse: Diagnosis

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Skin diseases where pruritus is an important feature are very common in many animal species, including the horse. Equine pruritus is often manifested by rubbing, and less commonly stomping, biting, and head shaking or tossing. Itchy skin diseases can be frustrating and time-consuming to diagnose, as lengthy treatment trials may be required (e.g. hypersensitivities), and managing the patient's comfort in the short term without interfering with trials and tests may be challenging. Long-term control measures are however much more likely successful after a diagnosis has been confirmed, allowing more targeted treatment.

The most common pruritic skin diseases are often allergic or parasitic. Primary lesions are often few or absent; papules and erythema are often the most prevalent. Secondary lesions that often dominate and may mask primary lesions most commonly include alopecia, scaling, excoriations, and crusting from self-trauma; and lichenification and hyperpigmentation with chronicity. Skin biopsies are frequently unrewarding diagnostically in this group of diseases, as many pruritic skin conditions will result in very similar histopathology changes.

The prognosis is excellent for cure in most parasitic diseases with thorough treatment, and variable for allergic diseases; some are relatively easily controlled with symptomatic treatment, while others are more persistent and problematic. It is also important not to forget to remain alert for clues suggesting any of the classically non-pruritic skin diseases, which may rarely present with pruritus as a major feature (e.g. bacterial folliculitis, dermatophytosis, and dermatophilosis).

Skin diseases of consideration in the itchy horse are listed below. Some diseases listed are covered in notes for alopecic, crusting and scaling$^{\#}$ or nodular* skin diseases.

A) Hypersensitivities

Insect hypersensitivity

Atopic dermatitis

Food adverse reactions

Contact hypersensitivity (and irritants#)

B) Ectoparasites

Insect irritation, including equine midline dermatitis

Helminth dermatoses: pelodera, strongyloides

Mites: sarcoptes (exotic to Australia, except in pigs); environmental mites# (trombiculids, forage mites, poultry mites); chorioptes#, and psoroptes#

Pediculosis#

C) Endoparasites

Onchocerciasis

Oxyuriasis

D) Miscellaneous

Urticaria* (may be pruritic or non-pruritic; and associated or un-associated with hypersensitivities)

A) HYPERSENSITIVITIES

Of all the pruritic skin diseases this group is often more frustrating to manage long-term; however making a clear diagnosis is the first important step to guide the most appropriate treatment options.

1. Insect Hypersensitivity ("Qld Itch", "Sweet Itch")

Insect hypersensitivity is the most common allergic skin disease in the horse. It occurs worldwide and is best documented to *Culicoides* spp. (biting midges, gnats, sandflies), however may also occur to flies (e.g. black flies [*Simulium* spp.], stable flies [*Stomoxys calcitrans*], and possibly buffalo flies [*Haematobia irritans*]). Mosquitos and sandflies are potentially also associated with insect hypersensitivity. *Culicoides* spp. vary around the world, with *C. brevitarsus* the major species in Australia. There is confirmed cross-reactivity that likely is relevant across all *Culicoides* species. Insect hypersensitivity has a distinctly seasonal pattern in temperate climates (spring, summer and autumn), however is often non-seasonal in sub-tropical and tropical climates. There is a suspected genetic predisposition, with incidence higher in some breeds including quarter horses, German Shires, ponies, Arabians, and Icelandic horses, although insect hypersensitivity can occur in any breed. The typical age of onset is 3-4 years; however any age can be affected. Horses often have recurrent bouts of disease at similar times each year.

NB Presumed insect hypersensitivity and/or atopy has been reported in ***sheep*** as a seasonal pruritic dermatitis on the ventral chest and abdomen, udder/teats, and sometimes the face and pinnae. Insect hypersensitivity does not appear reported in production animals other than the sheep.

Clinical Presentation

Pruritus is often intense, and a key feature of disease. Horses often cause severe self trauma, and damage to any rugs worn, by rubbing on any available surfaces. Primary lesions are papules, and secondary lesions are mostly associated with self-trauma: poorly-demarcated alopecia, scaling, crusting, lichenification, hyperpigmentation, and broken hairs on the mane and tail. The distribution of lesions will reflect insect bite sites, so is somewhat dependent on insects involved. Classically with *Culicoides* spp. the dorsal midline, ears, mane, and tail are the major affected areas. Overseas a ventrally orientated distribution of lesions is reported, with lesions on the ventral thorax and abdomen, axillae, groin, and intermandibular space, however this form does not appear reported in Australia.

Differential Diagnosis

When pruritus is severe in typically affected areas, the major differentials include atopic dermatitis, contact dermatitis and food adverse reactions; and occasionally pediculosis. Mite infestations (chorioptes, trombiculids, poultry mites), will typically on affect the muzzle and/or lower legs, which are not classically affected by insect hypersensitivity.

Diagnosis

Insect hypersensitivity is often presumed based on typical seasonal pattern of pruritus and consistent lesions; however atopic dermatitis and possibly food adverse reactions may appear identical. Histopathology from skin biopsies is non-specific, with a superficial and deep perivascular to interstitial eosinophilic dermatitis that could be consistent with other hypersensitivities or external parasite infestations. Intradermal testing can provide supportive positive results at insect allergen injection sites, however false positive insect reactions have traditionally been common, and ideal insect allergen concentrations for skin testing have only recently been determined. Diagnosis of insect hypersensitivity relies on consistent historical and clinical findings, and a complete response to a thorough insect control trial. The authors preferred option is permethrin (e.g. Permoxin® spray, Brute® wipe-on) applied once to twice daily (early afternoon +/- dawn) to all affected areas for 4 weeks. Rugs and hoods can be helpful to limit exposed skin however spraying is still required adjacent to, and on exposed areas. Complete response, and ideally relapse on re-exposure, confirms the diagnosis. The trial is often very time-consuming for owners to complete, however is essential to confirm the diagnosis and ensure expensive and involved insect control measures are warranted.

2. Atopic Dermatitis

Atopic dermatitis in humans and animals is defined as an inherited predisposition to develop type I hypersensitivity reactions, with production of IgE antibodies to a variety of environmental allergens (e.g. pollens, insects, mould spores, dust mites). In horses, atopic dermatitis is well-recognised, however the incidence is unknown. The typical age of onset is 1-6 years, and mostly disease is seasonally recurrent and worsens with age. Thoroughbreds and Arabians have been proposed at increased risk; however there is no clear evidence for a breed predisposition.

Clinical Presentation

Pruritus is again a key feature, often intense, and at least initially associated with absence of visible skin lesions. Atopy may also present as urticaria, with or without pruritus, and may also be involved in at least some cases of chronic obstructive pulmonary disease (COPD).

Primary lesions of atopy therefore include wheals, and also probably papules. Secondary lesions consist of a variety of self-trauma lesions, including poorly-demarcated alopecia, scaling, lichenification, hyperpigmentation; broken hairs on mane and tail; also more well-demarcated areas of alopecia and scaling associated with secondary superficial bacterial infections. Lesions are most typically distributed on the face, pinnae, ventral abdomen, ventral thorax and legs; and less commonly on the lateral neck, mane, and tailbase.

Differential Diagnosis

When pruritus is severe in typically affected areas, the major differentials include insect hypersensitivity, contact dermatitis and food adverse reactions; and occasionally pediculosis. Mite infestations (chorioptes, trombiculids, poultry mites), will typically affect the muzzle and/or lower legs, but less commonly the other ventral body sites affected with atopy.

Diagnosis

Diagnosis requires a compatible history and clinical signs, and ruling out other possible differentials, especially insect hypersensitivity, and for non-seasonal signs, food adverse reactions. External parasitic skin diseases should be excluded by treatment trials if history is supportive (e.g. environmental mites; difficult to identify on affected animal). Intradermal testing in horses is now performed in many parts of the world. Positive intradermal results will support a diagnosis of atopic dermatitis and/or insect hypersensitivity, however firm diagnosis requires exclusion of other differentials. Recent and current studies are more accurately determining the most appropriate allergen testing concentrations, in order to minimise false positive results which have previously been problematic in equine intradermal testing. Intradermal testing is performed to identify the relevant allergens for each atopic individual, to allow allergen avoidance measures where feasible, and immunotherapy ("desensitising" or "allergy" vaccines) formulation.

Serum "allergy" testing, measuring allergen-specific IgE levels, is the next best option for formulating immunotherapy however some tests have very poorly repeatable results and specificity. Currently the serum allergen-specific IgE test preferred by most veterinary dermatologists in Australia is the Allercept® test developed by HESKA in USA, available through Gribbles Pathology. It detects species specific IgE via the high-affinity IgE epsilon (ε) receptor, giving it higher specificity than many previous tests. They offer an equine specific IgE Allercept®, which appears to give fairly accurate results. False positives and negative will still occur, and the intradermal test remains the gold standard. Allergen-specific IgE testing is a useful option where referral to a veterinary dermatologist for intradermal testing is declined by owners.

3. Food Adverse Reactions (Food allergy?)

Cutaneous food reactions are poorly documented and understood in the horse, although have been well-characterised in humans and some domestic animals, and some cases have been confirmed in the horse. Some reactions will have an immunological basis, while others are caused by toxic reactions or intolerances. Affected individuals are typically exposed to the same diet for some time (at least months) before clinical signs develop, thus an *absence* of recent diet changes does not preclude food reactions. Clinical signs may be seasonal or non-seasonal, depending on the allergens involved and consistency of feeding; seasonal diet variations are more frequent in horses than small animals. No age, breed or sex predispositions are reported. Young horses can be affected. Food reactions in the horse have been suspected or confirmed to barley, beet pulp, bran, buckwheat, chicory, clover, concentrates and supplements, malt, potatoes, lucerne, St John's wart, and wheat.

Clinical Presentation

Pruritus (multifocal, regional, or generalised) and/or urticaria may feature. Lesions more commonly occur on the face, neck, trunk and/or rump. Exclusive tail and perianal lesions have also been reported. A variety of secondary lesions occur from self-trauma; most typically poorly-demarcated alopecia, erythema and scaling; progressing to lichenification and hyperpigmentation with chronicity.

Differential Diagnosis

Atopy and insect hypersensitivity are the major differentials, although oxyuriasis should be considered for exclusive perianal lesions, and other parasitic diseases including pediculosis, environmental mites, and helminths less commonly.

Diagnosis

As for humans and small animals, a firm diagnosis of food allergy requires demonstration of resolution or significant improvement after completion of a novel-protein elimination diet, followed by relapse on provocative re-exposure. Elimination diets are particularly challenging in horses, as it is often difficult to source and exclusively feed a novel protein. A common approach is to feed a base food not previously fed (e.g. lucerne, oat, or timothy grass hay), and withhold all concentrates, additives and supplements. If a grain is also necessary, a pure grain (e.g. oats, corn) rather than a mix should be fed. If the chosen food is not truly novel to the horse undertaking the test diet, a 2nd round of the elimination diet, feeding an alternate base food to the first round, may also be necessary. The required duration of an elimination diet in the horse is currently unknown; with 4 weeks often suggested. Resolution of clinical signs during the diet, relapse with provocative re-exposure, and resolution again on avoidance will confirm the diagnosis.

4. Contact Hypersensitivity (Contact Allergy)

Contact dermatitis may be caused by an irritant (or non-immunological) response, or by a type IV or delayed hypersensitivity response, whereby an immunological reaction occurs to a specific hapten, usually a small, chemically reactive, lipid-soluble molecule that binds to a protein to form an antigen. A variable sensitisation period from 3-5 weeks up to 2 years or more is needed before the hypersensitivity response develops. Irritant contact dermatitis is the more common form, covered in ‘alopecic, crusting and scaling diseases’; however it will often be clinically similar to contact allergy. Few cases of true contact hypersensitivity are documented in horses. Cotton, chrome, and jute are documented causes, while pasture plants, bedding, numerous topical shampoos and insecticides, grooming aids, blankets and tack all implicated. A contact reaction requires direct contact between the offending agent and skin; hair protects against direct contact, while moisture (e.g. sweating) enhances it. Contact reactions (allergic or non-allergic) are therefore more common in horses than other animal species, as horses will readily sweat.

Clinical Presentation

Pruritus is variable, and may be intense. Alternatively pain may be evident with severe lesions. Unlike for atopic dermatitis and insect hypersensitivity, the skin will always have evident lesions with contact reactions; and most typically the skin changes are more prominent than they are for the former differentials. Primary lesions may include papules or vesicles, and secondary lesions range from erythema, scaling, and alopecia to erosions and ulcerations with crusting when acute, and lichenification and pigmentary changes when chronic. Lesions occur in readily contacted sites; most commonly the head, extremities, ventral body surfaces and tail region. The affected sites depend on the allergen e.g. muzzle and lower legs for pasture plants or bedding; the face and trunk for tack; and the face, neck, and ears for insect repellents and sprays.

Differential Diagnosis

A wider list of differentials is relevant to most potential contact hypersensitivity cases, including the other hypersensitivities (atopy, food, insect); parasitic diseases (chorioptes, environmental mites, and helminths for lower leg lesions; and pediculosis for trunkal lesions); and infectious diseases where alopecia, erythema and scaling are prominent and pruritus less severe (e.g. dermatophilosis, dermatophytosis, superficial bacterial pyoderma).

Diagnosis

Collecting a detailed and accurate history is often crucial for diagnosing contact hypersensitivity in the horse. Carefully questioning owners about applied products, including one's that have routinely been used without problems in the past, and potential environmental sources of allergen is paramount. Diagnosis of contact hypersensitivity in people, in which it is a very common disease, largely relies on contact patch testing, where panels of suspected allergens are placed in direct skin contact for 48 hours, and skin reactions evaluated after a delay phase to allow settling of irritant reactions. In the horse as for other veterinary species, there are no standardised patch testing kits available, and together with difficulties of maintaining allergen contact at fixed sites via bandaging, patch testing is rarely used in the horse. More commonly, identifying the suspect agent/s from a good history, followed by resolution on removal of the offending agent, and recurrence on provocative exposure will confirm a diagnosis. Resolution of clinical signs on withdrawal of allergens may take up to 14 days.

B) ECTOPARASITES

1. Insect Irritation

A variety of flies can cause annoyance and discomfort to many horses when present in large numbers, and allergic responses in some individuals even in low numbers. The most common species to cause problems in Australia are horse flies (*Tabanid* spp), which are most active on hot humid days; and stable flies (*Stomoxys calcitrans*), that are ubiquitous and feed during the day. Horn flies (*Haematobia irritans*), feeding on the ventrum in warm sunny weather, or the dorsum in cool wet weather; and black flies (*Simulium* spp.) that feed at dawn and dusk are far less common. *Culicoides* spp. feed at dawn and dusk, and in outbreak situations may cause annoyance for non-allergic horses, in addition to severe disease in allergic horses. House flies (*Musca* and *Hydrotaea* spp.) do not cause direct irritation as they lack biting mouth parts. *Equine ventral midline dermatitis* is seasonal dermatitis reported overseas associated with *Haematobia irritans* (horn flies) and *Culicoides* spp. (gnats, sandflies). Horn flies are not common in Australia, and this disease appears not to occur here.

Clinical Presentation

Pruritus is frequent, and occasionally pain. Primary lesions are papules and wheals, which are most common on more sparsely-haired areas (face, ears, neck, ventrum, legs); and the dorsum.

The equine ventral midline dermatitis is most common in horses >4 years of age, although the majority of horses in one area will be affected; pruritus varies from intense to minimal; and classical lesions are well-demarcated areas of punctuate ulcers, haemorrhagic crusts, lichenification, and alopecia on the ventral midline.

Differential Diagnosis

As for hypersensitivities.

Diagnosis

The history of most horses in a group affected, consistent climatic and environmental conditions, and observation of flies outbreaks usually readily confirms the diagnosis.

Management

Control is by regular use of insect repellents (e.g. permethrin) and removal/reduction of breeding sites in the environment where possible. Knowledge of the fly species involved, their preferred breeding sites, and preferred times of feeding are helpful. (See treatment of Qld itch and atopic dermatitis for more details). Irritation rapidly subsides as insects die.

2. Helminth Dermatoses

Larvae of *Stronglyoides westeri*, a common small intestinal nematode of horses, and *Pelodera stonglyoides*, a free-living nematode found in damp soil and decaying organic matter, will occasionally invade percutaneously, typically under moist unhygienic conditions. Skin in contact regions is affected (lower legs, muzzle) with a pruritic dermatitis characterised by papules, alopecia, scaling crusts, and ulcers. Demonstration of larvae in skin scrapings (*Pelodera* typically numerous), or within hair follicles (*Pelodera*) or dermal granulomas on histopathology of skin biopsies is diagnostic. Treatment involves routine anthelmintic therapy for *Stronglyoides*, and cleaning the environment.

3. Mites - Sarcoptes (*Exotic**)

Sarcoptes scabiei mites have been eradicated in many parts of the world in horses and production animals, except for ***pigs***, where infection is very common. In **horses*** infection is extremely rare worldwide, although previously common: mites have been eradicated from many countries including USA and UK, and have never been present in Australia. **Cattle**, **goats**, **sheep** and **alpacas** are affected by *Sarcoptes scabiei* mites (*var capri*, *var ovis*) in some parts of the world, and appear not to be present in Australia. Sarcoptes mites are very contagious, and cause an extremely pruritic dermatosis with similar signs across all animal species.

Clinical Presentation

Primary lesions are papules, and prominent yellow-to-white adherent fine scaling with chronicity. Secondary lesions include poorly demarcated alopecia and excoriations from self-trauma. Pruritus is intense, and a key feature of disease. Lesions most typically affect the head, including pinnae, and neck in all species, but can be generalised.

Pigs The most common form of disease occurs in young growing pigs, with acute papular and self-trauma lesions, that progress from localised on the face most typically, to be generalised. A less common severely hyperkeratotic form occurs in multiparous sows or debilitated adults, with severe thick scaling to crusting.

Differential Diagnosis

The severe pruritus and papular to scaling dermatitis are usually characteristic, especially when occurring in pigs, however other ectoparasitic infections may occasionally mimic disease (e.g. pediculosis)

Diagnosis

Demonstration of typical sarcoptid mites in superficial skin scrapings is diagnostic, however mites may be sparse, and negative scrapings do not preclude a diagnosis.

Management

Ivermectin is likely very effective (200ug/kg orally once weekly for 4 weeks). All in-contact animals must be treated.

C) ENDOPARASITES

The major diseases in this group are now very rare in Australia, although prior to the development of ivermectin were important diseases worldwide.

1. Onchocerciasis

Onchocerca spp. are common filarial nematodes of horses. *O. cervicalis* and *O. gutturosa* have been associated with cutaneous disease in Australia. Adults live in the ligamentum nuchae, producing microfilariae which migrate in connective tissue; in skin to the upper dermis, particularly on the ventral midline. *Culicoides* spp. are vectors, and disease incidence may be higher in summer. Although infection is common, clinical disease is rare, and proposed due to hypersensitivity. Affected horses are usually > 3-4 years old; with a poor worming history.

Clinical Presentation

Pruritus ranges from mild to severe. Lesions are typically secondary: poorly-demarcated alopecia, scaling, erosions, ulcerations, crusting, and hypopigmentation; distributed on the ventral abdomen, chest, head, and neck.

Ocular lesions may occur concurrently: keratitis, depigmentation, conjunctival papules. In cattle, onchocerciasis is a non-pruritic nodular skin disease, detected more at slaughter.

Differential Diagnosis

Insect hypersensitivity, atopic dermatitis, food adverse reactions, insect irritation, mites infestations (environmental; sarcoptes (exotic)), pediculosis, and helminth dermatitis.

Diagnosis

Diagnosis can be difficult; and treatment trials are often indicated. Microfilaria (0.2mm long) can be demonstrated in skin scrapings, direct impression smears, or in macerated tissue biopsies after incubation in saline (37°C for 10-15mins). Skin biopsies for histopathology, revealing superficial dermal eosinophilic inflammation associated with microfilaria, are required for confirmation. Multiple samples may be required to demonstrate microfilaria, which tend to distribute in pockets.

Management

Oral ivermectin (200ug/kg) and moxidectin (400ug/kg) are very effective at killing microfilaria; typically only one treatment is required. An ocular examination is important prior to treatment, and concurrent glucocorticoids often recommended initially due to frequent exacerbation of cutaneous and ocular lesions associated with microfilarial death.

2. Oxyuriasis

The nematode *Oxyuris equi* (pin worm, thread worm) infests the caecum and large colon of horses. Cutaneous disease is associated with female nematodes crawling from the anus onto the perineum to lay eggs, producing perianal and tail pruritus. Disease is rare, and associated with a poor worming history, and often stabling.

Clinical Presentation

Patchy alopecia of the perianal areas and tail base, and broken tail hairs is the most frequent presentation. Pruritus varies from mild to severe.

Differential Diagnosis

Food adverse reactions, insect hypersensitivity, atopic dermatitis, and pediculosis are the major differentials.

Diagnosis

Tape preparations from the perianal area reveal characteristic triangular operculate eggs.

Management

Routine anthelmintics are effective. Stable hygiene should be improved.

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Chapter 6

Insect Hypersensitivity (QLD itch) & Atopic Dermatitis: Treatment Options

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Of all skin diseases, hypersensitivities can be one of the most frustrating to manage long-term, and within this group for the horse, both insect hypersensitivity and atopic dermatitis may be challenging. As previously discussed, ensuring an accurate and firm diagnosis is the first paramount step in any management plan. From there, a number of treatment options may often be considered, some of which may be impractical in certain situations and many that will have individually variable effects. The goal for the clinician and dermatologist alike is to find the safest, achievable, and most efficacious treatment plan for each individual patient, while taking in to account restrictive factors such as finances and performance needs.

INSECT HYPERSENSITIVITY (QLD ITCH)

Just to recap, insect hypersensitivity is reported as the most common allergic skin disease in the horse and is best documented to *Culicoides* spp., but may involve black flies [*Simulium* spp.], stable flies [*Stomoxys calcitrans*], and possibly buffalo flies [*Haematobia irritans*]) or mosquitos. Pruritus is a key feature of disease, along with self-trauma lesions typically including patchy alopecia, scaling, and lichenification, predominantly on the dorsum +/- head, and broken mane and tail hairs. Signs will mostly be seasonal associated with peak insect populations in temperate areas, however are often all year round in the tropics. A diagnosis of insect hypersensitivity is confirmed by resolution of pruritus after an intensive 4-week insect control trial.

For all hypersensitivities, avoidance of the allergen when possible is the ideal management plan. This holds true for insect hypersensitivity, and currently insect avoidance remains the mainstay of treatment. Symptomatic treatment is rarely very effective, as the typical degree of pruritus, limited drug choices, recurrent or persistent nature of disease, and tendency for disease to progress each year create great treatment challenges.

Mainstay of Treatment: Insect control, Insect control, Insect control!

Measures to reduce insect populations and/or avoid insect exposure are *essential* for management of insect hypersensitivity in the horse. Treatment of un-rugged grazing horses is extremely difficult. Effective insect control measures require some understanding of insect biology (see below), and ideally confirmation of which insect/s are involved (by intradermal testing, or perhaps fairly accurate with careful observation/insect trapping).

Insect control measures should ideally include:

a) Use of rugs, hoods

Rugs, neck rugs, and hoods are ideally worn continually during the insect season to limit access to biting insects: the more the body is covered, the less it can be bitten! The challenge initially is often to prevent destruction of rugs associated with severe rubbing until the pruritus eases; the options are to remove all access to rubbing posts/trees etc. (e.g. electric fences) or treat symptomatically to reduce the pruritus sufficiently first, until rugs can be worn without damage.

b) Insect repellent sprays

Synthetic pyrethroids appear to be the most widely accepted insecticides of value for control of insect hypersensitivity in the horse, especially permethrin, which is available as an aqueous spray (e.g. Permoxin®), oil-based sponge-on (e.g. Brute®), or pour-on product (e.g. Swift®). Being oil-based, Brute® is may be more water-repellent during times of frequent rainfall. Other potentially more residual products (e.g. deltamethrin pour-on) used for insect control in cattle may be helpful.

Insect repellent spray or wipe-on should be applied to all exposed skin, and be timed prior to major insect feeding times. Ultimately frequency of application will depend on other measures in place and current insect populations.

c) Measures to reduce insect populations

This step also requires initial identification of the allergenic insect/s, together with an understanding of their biology.

Culicoides spp. are tiny flies, 1-4mm long that feed at dawn and dusk, and breed in damp decaying vegetation or manure.

Stable flies (*Stomoxys calcitrans*), are ubiquitous, 5-8mm long, feed during the day, and breed in wet/decaying straw, bedding, manure, wet grass clippings, compost; seaweed.

Simulium spp. (black flies) are 1-5mm long, feed at dawn and dusk, and breed in running water. They are less commonly a problem in Australia; if so, found in wet areas.

Tabanid spp. (march flies) are large flies (up to 25mm) with painful bites, which are most active on hot humid days, and breed on vegetation near water sources.

Haematobia irritans (buffalo flies) are more prevalent in tropical areas

A common theme is water, vegetation, and manure: thus insect populations may often be reduced by removal of sources of stagnant water, decaying vegetation, and manure.

Control measures may also include **special housing/conditions**:

- stabling at high risk times - e.g. dusk and dawn for *Culicoides* spp, with:
    - ceiling fans - many insects don't fly as readily in windy conditions, simulated by the fans, including *Culicoides* spp.
    - fine-meshing – has to be very fine to keep out *Culicoides* spp.
    - sustained release insecticides

Alternative Treatment Options: Immunotherapy?

Immunotherapy for insect hypersensitivity is currently not widely available, and response is unclear. One early study in USA (Barbet, 1990) showed no benefit. However, a more recent study in British Columbia (Anderson, 1996) using higher doses of allergen showed more promise. Unfortunately Culicoides antigen is not readily commercially available as yet, and even where available is expensive: the cost of high weekly doses used in British Columbian study would largely be prohibitive. Comparing to flea hypersensitivity in dogs which has many shared pathophysiological features, immunotherapy using a variety of protocols and doses has largely proven ineffective in this disease.

Symptomatic Control Options

Practical options are largely limited to glucocorticoids. Oral prednisolone (anti-inflammatory doses e.g. 0.5 mg/kg sid) or injectable dexamethasone (0.05-0.1mg/kg SC) can give short-term relief when pruritus is severe. It is important to realise they won't always be effective, that side effects are frequent with long-term use, and that severe side effects may occasionally occur very quickly, even at relatively low doses: muscle wasting, weight gain, exercise intolerance, laminitis?

ATOPIC DERMATITIS (AD)

AD in horses is well-recognised, however the incidence is unknown. The typical age of onset is 1-6 years, and disease is mostly seasonally recurrent and worsens with age. Thoroughbreds and Arabians have been proposed at increased risk; however there is no clear evidence for a breed predisposition. Pruritus is again a key clinical feature, and at least initially associated with absence of visible skin lesions. Lesions are most typically distributed on the face, pinnae, ventral abdomen, ventral thorax and legs; and less commonly on the lateral neck, mane, and tailbase. Atopy may also present as urticaria, with or without pruritus, and may also be involved in at least some cases of chronic obstructive pulmonary disease. Diagnosis requires a compatible history and clinical signs, and ruling out other possible differentials, which mostly includes insect hypersensitivity for the horse, and less commonly food adverse reactions, or some external parasitic diseases (e.g. environmental mites excluded by treatment trial as difficult to identify on affected animals).

Treatment options for AD in dogs and cats are well-reported, and similar options are likely relevant for horses, although little scientific literature is available. Most successful programs in other species are multifaceted, taking into account numerous factors that may be relevant to disease, including barrier function defects, secondary microbial infections, drying or irritant products, allergens, stress factors and performance needs.

A) Minimise Allergen Exposure Whenever Possible

Although allergen avoidance is an ideal goal, it is rarely sufficiently possible in AD to alter the course of disease, and there are even further challenges in the horse with AD. It is vital to know which allergens are relevant to each patient before contemplating avoidance, as there is a broad range of potential allergens that will be relevant in very variable combinations. The main groups of airborne allergens are pollens, insect particles, dust & storage mites, and mould spores, and effective reduction measures are usually only possible for dust mites and mould spores, and extremely difficult for pollens and insect particles. The relevance of dust mite allergy to atopic horses is currently unclear, although a recent study by the author has confirmed potential exposure of horses to dust mites from horse rugs (data submitted for publication). Much information is available in the human medical literature on avoiding or minimising exposure to dust mite allergens, and regularly exposing horse rugs to sunlight and drying may potentially provide very effective control if dust mite allergies are relevant to horses. Mould allergy in equine AD in Australia appears very rare, and pollen allergy very consistent (unpublished observations), further limiting practical avoidance control measures for equine AD.

B) Allergen-Specific Immunotherapy

i. What is it?

Allergen-specific immunotherapy is the process of administering increasing amounts of a combination of relevant allergens in pre-determined concentrations, via regular subcutaneous injections. The appropriate allergens must be identified by allergen testing. The aim is to alter the immune-response, from the T-helper 2 lymphocyte-dominated allergic reactions, where pruritus-inducing mast cells, eosinophils, and IgE antibodies play important roles, to a T-helper 1-dominated response where they don’t. IT has been shown in studies in humans, dogs, cats, and horses to have significant benefits in some patients with atopy and/or urticaria. Success rates reported in horses are 70-80% with good responses, measured by a marked reduction in the need for other symptomatic control measures. Unlike symptomatic treatment options, immunotherapy has the ability to alter the allergic response, effectively “reducing” the allergy. It takes 6-12 months to begin helping, and should ideally be considered a minimum 2-year program. The best allergen concentrations/combinations, injection schedules, and concurrent treatments vary for every patient, and the greatest success rates are reported when immunotherapy is closely monitored and altered as indicated by experienced dermatologists.

In horses immunotherapy is generally recommended when:

- Allergy is severe
- Allergens are hard to avoid (e.g. pollens); or reducing allergen exposure (e.g. moulds) is only partially effective
- Symptomatic medications do not work, or cause side-effects
- It is preferred to avoid medications

ii. How is it done?

The first step is to accurately *identify the relevant allergens*. This requires either intradermal allergen testing or serum allergen-specific IgE testing. Intradermal testing remains the gold standard; however allergen-specific serum IgE testing is a useful option where referral to a veterinary dermatologist for intradermal testing is impractical due to distances, or declined by owners.

Intradermal allergen testing involves the intradermal injection of multiple allergenic extracts (pollens, moulds, dust and storage mites, and insects), together with positive and negative control substances, and watching for the development of hive-like “wheal and flare” reactions ~ 10-20minutes after injection. We typically sedate horses with Detomidine® (opiates and ACP can interfere with test results, so are avoided), and an area ~ $10cm^2$ is clipped on the neck or lateral shoulder. Care must be taken to standardise the injection technique and volume. Histamine and saline are used as positive and negative controls respectively, to which allergen reactions are compared. Reactions are scored subjectively, based on wheal size, erythema and turgor, typically on a scale of 0-4, with 4 representing a strong positive.

iii. Is intradermal allergen testing accurate in the horse?

The accuracy and relevance of intradermal allergen testing in horses has previously been questioned due to a high level of false positives reactions. Recently a number of studies in normal horses, including one performed at the Camden Campus of the University of Sydney relevant to Australia, have improved the specificity of intradermal testing in horses by clarifying the best concentrations of allergens to use for testing. In the Camden study responses were evaluated to a range of allergens (pollens, moulds, dust and storage mites, and insects) in normal horses, and at the identified appropriate testing concentrations, strong reactions to allergens were not seen in any normal horses. Testing was repeated over three seasons to assess repeatability and any seasonal variations. Strong reactions to variable combinations of allergens at the appropriated concentrations are typically very clear and easily identified in allergic horses undergoing intradermal testing (unpublished observations). Delayed reactions at 4-6 hours post-injection were previously considered important; however were found to probably represent irritant reactions in the Camden study of normal horses. It is important drugs potentially interfering with skin test reactions, including corticosteroids (for at least 2 weeks; may be shorter withdrawal in horses than dogs and cats) and antihistamines (for 2 weeks) are withdrawn adequately prior to testing.

C) Symptomatic Therapy

Apart from allergen avoidance and immunotherapy, symptomatic treatment is the only other option. It is variably effective for atopic dermatitis in the horse. Although the tendency is always to use symptomatic treatments reactively (e.g. when there are visible lesions and/or pruritus), it is more ideal to use them preventatively (i.e. keeping up a regular program that helps to keep allergy signs fairly stable, and minimise flares of disease).

Safer long-term options include:

i) *Antihistamines* – e.g. chlorpheniramine 0.25-0.5mg/kg bid; may sedate and/or interfere with performance

ii) *Fatty acids* - e.g. flax seed oil, linseed oil, fish oil 1-2mls/kg sid

iii) Appropriate treatment of *secondary bacterial pyoderma* – as with small animals, this may complicate AD in some horses; topical 2-3% chlorhexidine solution, or oral TMS are indicated

iv) *Topical therapies:*

  a) Cleansers - regular well-chosen shampoo therapy may help horses with AD. Antibacterial/antifungal shampoos are ideal if there are regular secondary bacterial and/or yeast infections: Pyohex® or Pyoben®. Soothing shampoos are otherwise indicated: Aloveen®, Episoothe®, PAW sensitive skin® (no sulphates) are all potential off-label options that may help. Avoid drying shampoos in most cases: tar-based, selenium, benzoyl peroxide. The recommended frequency of bathing depends on the clinical signs: it can be done as frequently as daily, assuming sustained good response; however once to twice weekly is often more practical.

  b) *Moisturisers* - are one of the mainstays of symptomatic treatment for humans with atopic dermatitis, and may be helpful in horses too. Alpha Keri® bath oil is one of my preferred options for the horse. Choices include: *Humectants*: attract water from deep within the skin towards the surface e.g. carboxylic acid, lactic acid, urea, sodium lactate (non-oily) OR prevent water loss via transpiration e.g. propylene glycol, glycerine, polyvinylpyrrolidone, sorbolene.

Emollients: fill spaces between keratinocytes with oil e.g. Alpha Keri® bath oil, variety oils (almond, corn, coconut, olive, peanut, safflower, sesame), animal fats (e.g. lanolin), hydrocarbons (e.g. mineral oil, paraffin oil, petrolatum)

Emulsifiers: help distribute oils in a water solution (e.g. acetyl alcohol, laureth-5, lecithin, steric acid, stearyl alcohol)

c) *Glucocorticoids* - topical forms are also one of the mainstays of treatment for atopic dermatitis in humans, and very valuable in some atopic animals. They are most suited to relatively hairless and at least somewhat localised itchy areas. Choices: More potent steroids most effective e.g. Aristocort® (triamcinalone), Elocon® (mometasone) – can use daily 3-4 weeks to settle severe itch, then ideally no more then 2-3 times weekly longer-term (they may thin skin and increase risk infections). Topical Cortavance ® spray is a potential off-label option easier to use on haired skin, and with less skin atrophy effects. NB These options are much more effective than most less potent veterinary preparations e.g. hydrocortisone or prednisolone creams, lotions, and ointments, however also significantly more expensive. All are absorbed best when applied to moist skin; try to ensure no licking for 10-minutes after application.

The safer options are unfortunately only variably effective, and rarely spectacularly, especially for severe pruritus. They are often best used to help keep the allergy signs settled after initial settling with more potent products (e.g. systemic glucocorticoids). When ineffective alone, such safer options may still reduce the need for more potent therapies including systemic glucocorticoids.

More efficacious options - Although more reliably effective, glucocorticoids can have potentially serious short and long-term side effects. Prednisolone and dexamethasone have been used, as for insect hypersensitivity, to reduce severe pruritus. Oral prednisolone (anti-inflammatory doses e.g. 0.5 mg/kg sid) or injectable dexamethasone (0.05-0.1mg/kg SC) can give short-term relief when pruritus is severe. Doses should be reduced to the lowest effective levels, ideally administered on an alternative-day basis or less, and potential side-effects discussed with owners when used longer term.

Cyclosporine has made management of severe, poorly-responsive atopic dermatitis MUCH easier in both dogs and cats (off-label in cats). It is a potent immunosuppressive agent, although has a more restricted action than glucocorticoids, suppressing T-lymphocytes in particular. Unfortunately the expense of this drug makes its use in the horse for AD cost prohibitive.

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Chapter 7

Pastern Dermatitis: Approach to Diagnosis and Management

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INTRODUCTION

Pastern dermatitis (also known as “greasy heel”, “mud fever”, or “scratches”) is an extremely common entity in the horse, caused by multiple potential underlying diseases that often produce very similar clinical lesions. Diseases of this area may be related or linked to disease processes elsewhere in the horse, or they may be confined to the coronet and pastern alone. This part of the horse’s leg is subjected to changeable environmental conditions and has diseases which can be difficult to positively identify and treat. Some are found as part of a general disease pattern such as dermatophilosis, occasionally dermatophytosis and less commonly, vasculitis. The remainder are open to speculation and require further investigation.

Pastern dermatitis should be investigated as for dermatitis elsewhere on body, and all the principles of a logical diagnostic approach to skin disease definitely apply.

The *most common* diseases causing pastern dermatitis include:

1. **Superficial bacterial pyoderma** (very common secondary and perpetuating factor)
2. **Dermatophilosis**
3. **Chorioptes** (mainly heavy-feathered lower legs)
4. **Physical factors** (e.g. insect bites, wetting/skin maceration, mild repetitive trauma, irritants)
5. **Contact irritants** (e.g. plants, topical treatments)
6. **Vasculitis** (possibly photo-activated)

CLINICAL PRESENTATIONS

For all differentials the types and distribution of lesions may appear very similar. Pastern dermatitis may affect single or more frequently multiple limbs, palmar or dorsal surfaces or both (mostly starting on the palmar surfaces), with non-pigmented skin often more severely affected than dark skin. Primary lesions are rare, but may include papules, pustules, and vesicles. Secondary lesions are more common, including variable combinations of alopecia, erythema, and scaling with mild cases, progressing to ulceration, crusting, oozing and swelling in more severe or chronic cases. Severe chronic lesions may lead to chronic granulation tissue: so-called “grapes”.

CHOICE OF DIAGNOSTIC TESTS

With the above common differentials in mind, the most appropriate initial diagnostic tests are surface cytology (impression smears from moist lesions; tape preparations from dry lesions), superficial skin scrapings (for chorioptes, or occasionally environmental mites), and sometimes skin biopsies. Treatment of secondary bacterial pyoderma is important in most cases before considering biopsy, as it is can cause marked secondary changes on histopathology that may mask primary changes.

MANAGEMENT TIPS

If a primary diagnosis is not apparent with initial tests, and disease is not severe or unusual, symptomatic treatment is a reasonable initial option. Important points are:

1. **Treatment of secondary surface bacterial infections** is often important: (see alopecic, scaling, and/or crusting skin diseases for more details). Linda’s preference for antibacterial treatment is topical 2-3% chlorhexidine solution (not scrub), applied as a twice daily spray to affected areas for a minimum of 3 weeks. As an alternative, especially with eroded to ulcerated areas, topical 1% silver sulfadiazine cream (Silvazine® - discontinued; replaced by Flamazine®) is another option. Systemic antibiotics may be indicated in severe infections associated with limb swelling, and are ideally guided by bacterial culture and sensitivity testing, although oral trimethoprim sulfur is the main practical option considering a minimum of 3-weeks

treatment is advised. Ideally tissue biopsies collected with sterile technique are provided for culture, however surface swabs (after initial cleaning of debris with saline) are often adequate, especially if surface cytology reveals a largely monomorophic population of intracellular bacteria (typically cocci: mostly *Staphylococcal* spp.). If bacteria present are pleomorphic (cocci +/- rods, of variable appearance) surface culture is likely to be unrewarding.

2. **Minimising irritants and skin trauma** Many topical preparations used by horse owners and sometimes veterinarians can irritate the skin, and should be avoided. This includes iodine in some horses (less commonly chlorhexidine!), purple sprays, sulfur products, sump oil, and many of a myriad of other products that may be applied. It also includes avoiding rough or constantly wet pastures whenever possible. Beware of stabling unless stable hygiene is very good as wet unhygienic manure and urine loaded straw or shaving is BAD
3. **Maximising skin surface health** Topical moisturisers may help to retain skin moisture by repairing damaged barrier function, particularly for dry, scaling skin. Alpha keri® bath oil or lotion is one easily applied option. Sorbolene cream, or QV lotion are other options. Oral fatty acid supplements may also be considered (see atopic dermatitis treatment for details). When all else fails don’t forget soft Zinc cream
4. **Minimising sun exposure for non-pigmented legs** At least in the short-term until good hair regrowth occurs, solar damage may perpetuate initial inflammation. Restricting outdoor exposure at the peak times of day via stabling is ideal. Bandaging of lower legs can be considered, however exacerbation of secondary infections can occur in moist environments. Another strategy is to make up large trouser legs to cover the lower limbs these can be fastened to loose day rugs ,duct tape to upper leg is not a great idea

Following this guide will often allow good control or resolution of signs when primary factors are relatively insignificant (e.g. repetitive skin trauma, maceration from frequent wetting). If disease persists despite adequate antimicrobial treatment, further consideration of primary differentials is important, which begins with a reassessment of all historical data, repeating surface cytology tests and scrapings, and often collection of multiple skin biopsies.

DIFFERENTIAL DIAGNOSIS

1. Physical Causes:

a) Contact dermatitis: primary irritant or allergic contact dermatitis. Irritant substances or allergens (e.g. clover) contacting the pastern area. All four extremities are usually involved.

b) Actinic dermatitis: includes solar damage (sun-burn), or photosensitisation – both will involve other non-pigmented exposed areas where present common with echium poisoning of the liver

2. Infectious Causes:

a) Bacterial

- i) **Secondary bacterial pyoderma** (typically *Staphylococcal* spp.) is very common; diagnosed by skin surface cytology, or occasionally requires response to a treatment trial
- ii) **Dermatophilosis** is less common on the pasterns, but does occur; consider in wet environments or with previous history of disease in affected horse/property; diagnosed by surface cytology

b) Fungal – **Dermatophytosis** is rare on the pasterns, and usually due to *M. gypseum of T.verrucosum(horses used in feedlots)* Fungal culture is important to confirm, but may be difficult; a clinical clue is well-demarcated borders to alopecia, at least in some areas.

c) Parasitic

- i) **Chorioptic mange** is a MAJOR differential for any pastern dermatitis in well-feathered breeds (Shire, Draught), and is occasionally found in other breeds (mostly in-contact with high risk breeds); pruritus of lower limbs is a clue (foot stamping/biting), especially in multiple in-contact animals, however some are minimally pruritic; superficial skin scrapings, collecting ample surface scale are mostly diagnostic; tape preparations may reveal mites and are often much easier to perform in this location
- ii) **Environmental mites** e.g. trombiculids, forage, or poultry mites are typically suggested by a history of multiple affected animals in a predisposed area, possible seasonal

recurrence, and the presence of obvious pruritus. Mites are often difficult to find, and diagnosis is more typically based on consistent history, and/or finding mites in the environment.

iii) **Helminth dermatitis** *Pelodera strongyloides,* a free-living nematode found in damp soil and decaying organic matter; or *Stronglyoides westeri* larvae, a common small intestinal nematode of horses, will occasionally invade percutaneously, typically under moist unhygienic conditions. The muzzle is also classically affected, and pruritus is a feature. Diagnosis is via skin scrapings or biopsy; however suspected in poor environmental conditions and/or with poor anthelmintic history. Good trick to do if you suspect either of the larvae to be present in old handling yards after prolonged wet weather place the horse leg in a large plastic (garbag) bay and wash leg with small quantity of water and use binocular mic to check for free swimming larvae

3. Immune-Mediated Causes:

a) **Vasculitis** occurs in a number of forms in horses, including pastern dermatitis. The disease may be more common than realised, affecting young as well as mature horses and having no sex predilection. Non-pigmented extremities are most frequently affected however occasionally only one leg is affected even when other legs are non-pigmented. The disease usually occurs in summer in regions with plentiful sunlight, but has also been reported in northern hemisphere in winter with little solar exposure. It is a sporadic disease affecting individual horses. Medial and lateral aspects of the pastern are the most common sites. Records of affected horses also indicate no known contact with photosensitizing compounds and liver function has been normal.

Early lesions include clearly demarcated regions of erythema, oozing and crusting. Later lesions show erosions and ulceration with some oedema of the affected limb (more extensive than expected for lesion size). Chronic lesions may have a warty type surface resisting removal, and affected legs tend to be more painful than pruritic.

Skin biopsies are required for diagnosis, however vasculitic changes are transient and dynamic, and multiple samples are important early in the course of disease or at times of acute flares to increase diagnostic yield. Liver function tests should be performed to exclude liver disease causing photosensitisation in all confirmed cases. Vasculitis is often a secondary disease in many species, so other underlying differentials, including secondary bacterial infections, should be considered. Purpura haemorrhagica and strangles (*Streptococcus equi*) vasculitis may also affect the pasterns, although classically involve other areas as well, including the fetlocks, lips and periorbital areas.

Affected areas should be protected from ultraviolet radiation via stabling, leg bandages, or sun block. Large doses of corticosteroids (e.g. prednisolone 1-2mg/kg twice daily) for up to 2 weeks are reported effective in confirmed cases, with doses then gradually reduced to every other day over the next 4 weeks. Emollient creams or keratolytics such as salicylic acid may also help symptomatically. There may be occasional regression when treatment stops, requiring a further course of corticosteroids, or continued alternate day therapy at the lowest effective dose.

b) **Pemphigus foliaceus** will rarely present localised to the coronary band. Crusting will normally be a prominent feature, and early pustules may be evident. Biopsy is essential for diagnosis.

4. Miscellaneous Causes:

a) **Coronary band dystrophy** is reported predominantly in mature and draught bred horses. Aetiology is unknown: it may be a defect in the cornification of the coronary band. All four hooves are affected with proliferation and hyperkeratotic changes to the coronary band, ergot and chestnut. Wall and severe coronary band changes are also seen. Cracks and fissures can bleed or ooze serum. Diagnosis is based on clinical signs and the elimination of all other causes; in particular in these breeds, chronic chorioptic mange and often concurrent chronic secondary bacterial pyoderma must be excluded by careful skin scrapings in multiple contact animals. Histopathology is not well documented. Treatment has involved removal of excessive horn and application of emollients to the coronet.

b) **Proliferative hyperplastic pastern dermatitis of draught horse breeds**: may be similar to above; is an idiopathic entity with extensive lesions including marked leg swelling, lichenification, excessive scaling, and chronic hyperplastic changes.

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Chapter 8

Interactive Case Sessions: Equine and Large Animal Skin Disease

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CASE 1

Signalment:

1 month old, female, Standardbred foal

Presenting History:

1 week history of crusts developing on the muzzle and periocular areas, with some more scattered lesions also on the neck and trunk. Sudden onset of lameness and elbow swelling in last 24 hours.

Further Questions?

Differential Diagnoses:

Diagnostic Tests:

Diagnosis and Outcome:

CASE 2

Signalment:

4 year old male Alpaca

Presenting History:

6 month history of poor haircoat with patchy alopecia and scaling, with no apparent pruritus. Also poor apparent fertility.

Further Questions?

Differential Diagnoses:

Diagnostic Tests:

Diagnosis and Outcome:

CASE 3

Signalment:

Group of 29 Standard bred weaners, yearlings and 2yr olds.

Presenting History:

A smouldering outbreak of strangles occurred in this group of horses A variety of weeping sores, around pastern, cannon and as high as the stifle occurred. Vaccination PLUS some weird animal husbandry led to 2 yearlings being destroyed and others having prolonged recovery.

Further Questions?

Differential Diagnoses:

Diagnostic Tests:

Diagnosis and Outcome:

CASE 4

Signalment:

A poorly grown yearling TB colt.

Presenting History:

The colt was presented with multiple subcutaneous swellings over the body which ruptured and discharged thick creamy pus. The yearling had a history of poor growth and had been stabled or yarded for most of his life. He was wormed by the owner with paste wormers on a couple of occasions.

Further Questions?

Differential Diagnoses:

Diagnostic Work Up:

Diagnosis and Outcome:

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Chapter 9

Dermatology: That Was Then & This Is Now

Greg Burton FACVSc (Dermatology)

All of us that work in private practice understand that veterinary science is a reactive job. Time pressures are our number one source of stress. Finding time to update our knowledge is difficult. Continuing education events, such as the one you are attending now, are critical. They are a concentrated, time efficient, method of gaining expertise from specialists. It would take many hours, per subject, trawling through the literature to acquire this information and then it would come without the interpretation of clinical experience. Imagine if our knowledge base was not updated and remained at the level of our graduation from Veterinary School. As way of an introduction into what we will be covering in the next 3 days, and to highlight the importance of continuing education and some significant advances in recent times, I thought I would take you back to my new graduate knowledge (early 1980's) and see how far we have come during my time as a veterinarian. For those more recent graduates in the audience the increased knowledge during your professional lifetime will be scary!

In 1981 the University of Sydney Post Graduate Foundation published a soft cover book titled ***Canine Dermatoses*** by Assoc Prof JM Keep "designed as refresher training, technical upgrading and modernisation" for the veterinary profession. Where applicable this will be our reference point for THEN knowledge and I will compare this information with what you are about to receive during the next 3 days.

FIRST PRINCIPLES

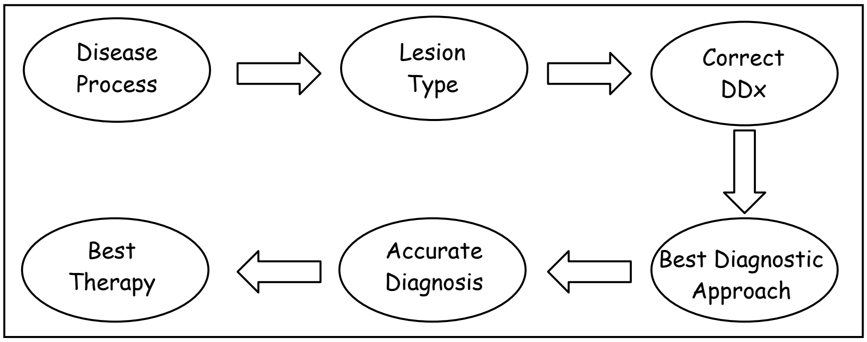
Pathogenesis:

THEN:

Aetiology was used interchangeably with pathogenesis. "Aetiology and diagnosis are inseparable. The practitioner must take every effort to understand the nature of the condition, to discover it's cause, and thereby establish the correct diagnosis”. Rational therapy requires and accurate diagnosis and empirical treatment frequently fails.

NOW:

This message has not changed. We have more tools now to allow us to better understand pathogenesis and patho-mechanisms of disease but we have always known how critical this is. No matter how much we fight it, the process (pathophysiology) of disease, is the cornerstone of good medicine. ALL our management decisions are going to be improved if we take a few minutes to consider the process. [1] This is because…



If you can recognise the lesion then often there are a limited number of processes that can create that lesion. Therefore there is a limited differential diagnosis list and from there the diagnostic process is not so daunting. This will be a message echoed a number of times during the next 3 days especially when we are dealing with species where we have limited knowledge as in the zoo animals.

OTITIS EXTERNA

THEN

Otitis externa was not covered in Canine Dermatoses 1981 although we all recognise the frequency in which dogs present with this symptom. Looking to the literature back then we knew:

i. Altered microclimate increases the risk of otitis externa.[2]

ii. *Otodectes* induce hypersensitivity reactions.[3]

iii. Otitis externa can be a sole clinical symptom in canine atopic dermatitis.[4]

iv. *Pseudomonas spp* commonly isolated from infected ears.[2]

v. Otoscopy is unreliable for establishing whether the tympanic membrane is intact. [5]

vi. Histological changes of the external auditory canal occur with chronicity.[6]

vii. About 50% of ear infections will be mixed infections.[7]

viii. Some antiseptics are ototoxic if the tympanic membrane is not intact. [8]

ix. Budding yeast were important in otitis externa.[9]

Back then we were starting to ask WHY do dogs get otitis externa, we were starting to understand the normal flora and how that changes with inflammation, the importance of preventing secondary changes and establishing the integrity of the tympanic membrane before treatment.

NOW

Since then there have been advances in imaging (video otoscopes, ultrasonography, computer tomography, magnetic resonance imaging) all of which have contributed to our knowledge in functional anatomy of the ear. There have been advances in microbial genotyping, toxin identification, innate and acquired immunological responses to microbes and the role of the epidermis in inflammation. There has been an explosion of otic preparations both antimicrobial and cleaning agents and increasingly there is the ability to assess safety of these preparations.

In the next few hours Linda Vogelnest, David Robson, Arthur House and myself hope to be able to answer for you many of the questions that were starting to be asked back in the 80s and give you a greater understanding of how the ear works, why things go wrong and how to not only better resolve the current otitis episode but also help minimise the risk of recurrence.

PRURITIC DISEASES

Atopic Dermatitis

THEN:

Atopic dermatitis is an allergic state with a genetic background initiated by inhaled allergens. Dachshunds, Wirehaired terriers and Poodles are predisposed. Clinical symptoms include rubbing or scratching at eyes, nose, axillae together with foot licking. Occasionally sneezing, coughing and rhinorrhoea are seen. Diagnosis is made by signalment, history, ruling out the differentials of folliculitis, allergic contact dermatitis, flea-bite dermatitis and scabies together with intradermal skin testing. Treatment is oral prednisolone 1 to 2mg/kg bid for 5 to 7 days and then the same dose given every second morning. Antihistamines do not work and immunotherapy is equivocal.

NOW

Wire haired terriers still are predisposed but Labradors have taken over the mantle as the pin up dog for canine atopic dermatitis. The classical presentation of atopic disease still involves face and feet but we also recognise a wider range of clinical patterns of atopic disease. Atopic dermatitis is a clinical diagnosis of exclusion and Mandy Burrows will takes us through the complexities of diagnosis. IgE testing, intradermal and serology, are supportive of a diagnosis of atopic disease but are essentially used AFTER a diagnosis has been made for the purpose

The biggest change since then has been an increase in our understanding of pathogenesis of canine atopic disease and this has lead to new treatments and changes in the way we manage this disease. Beth McDonald, Peter Hill and myself will be trying to convince you in the next couple of days that atopic dermatitis is not just an allergy but has significant skin barrier dysfunction contributing to the clinical features. That percutaneous absorption of allergens is the major pathway for both sensitisation and elicitation. That microbial colonisation of the skin can have a profound affect on the course of the clinical disease. That successful management requires addressing the skin barrier issues, controlling microbes and treating the allergic component. That allergen specific immunotherapy can be very effective when both case selection and allergen selection are carefully addressed AND that we need to start thinking more about treating our dogs topically for both safety and efficacy reasons. We will not be hiding the fact that there is still much we do not know and that we still have limitations in our ability to identify relevant allergens for immunotherapy. We will also be discussing some of the limitations of immunotherapy, potential advances in future immunotherapy and alternative treatments in the future.

Peter Hill will bring you up to speed on hypersensitivity diseases in the cat. Unfortunately that are not little dogs and what we know about dogs can not easily be extrapolated to the cat model.

FELINE MYCOBACTERIAL DISEASES

THEN

Feline tuberculosis due to *M bovis* and *M tuberculosis* was recognised but epidemiology data considered unreliable due to lack of accuracy of diagnostic tests. [10] *M lepraemurium* was suspected as an aetiological agent in feline leprosy due to successful transmission studies.[11] Feline leprosy was known to have a long incubation period and to present in Winter after Summer exposure. [12] Very little was known about treatment and there were a paucity of case reports of atypical mycobacteriosis to give the clinician meaningful help.

NOW

Improved sample collection, processing, laboratory techniques, culture media, PCR technologies and Richard Malik have lead to a much greater understanding. Mycobacteriosis in the cat is a far more diverse disease then we first thought. Richard will expand our knowledge on the all aspects of feline mycobacteriosis and help us make good therapeutic decisions on how to manage this difficult syndrome.

DEMODICOSIS

THEN

Aka follicular mange and “red” mange. The demodectic mite (*Demodex canis*) has been incriminated as the aetiological agent. Transmission is from the bitch to the puppies in the first few days of life. 13 “The mite is also found in dogs with healthy skin however, and so it’s role in producing the dermatitis of follicular mange is not known, but is probably due to a defect in the hosts immune system.” Diagnosis is made by skin scrapings and other folliculitis diseases need to be differentiated. Treatment options include 8% fenchlorphos solution and amitraz. Corticosteroids are contraindicated.

Studies have demonstrated that active pyoderma in demodicosis was associated with reduced lymphocyte mitogenic responses and this negative effect on cell mediated immunity resolved with resolution of the pyoderma. 14

NOW

There is still a lot that we do not know about this parasite but we do now recognise morphologically distinct types of *Demodex* mites that are associated with different clinical presentations. David Robson will update us on what is new in the world of *Demodex* including pathogenesis, identification of mites, clinical presentations and the treatments. There is no question that treatment options for this disease have come along way both in efficacy and safety. If you think you know all you need to know about demodicosis then think again. You will be surprised by how much you do not know!

ZOO ANIMAL DERMATOLOGY

THEN

Dissemination of information limited

NOW

Knowledge is still limited but most zoological gardens now have free and open exchange of information regarding disease. Treating zoo animals is a challenge in first principles. Linda Vogelnest and myself will present some cases that re-enforce the need for first principle approach when faced with the unknown. This is equally true whether the patient is a dog or a giraffe!

NOTABLE ADVANCES

Advances in knowledge and understanding of diseases reflect the work of some of our more prolific veterinarians such as Richard Malik (infectious diseases), David Lloyd, Ian Mason (ecology of skin commensals), Dufait, Ken Mason, Bond (recognition of Malassezia as a pathogen), Dan Morris (MRSA, Malassezia hypersensitivity, S. schleferi), Richard Halliwell, Thierry Olivry, Toshiroh Iwasaki (immune mediated diseases), Halliwell, Rosanna Marsella and the Task Force that included Ralf Mueller and Peter Hill among many others (canine atopic dermatitis), Maja Suter (keratinocyte biology and role in disease), Verena Affolter and Peter Moore (histiocytic diseases), Michael Day (immunology), Tony Stannard and Reg Pascoe (equine), Peter Ihrke, Doug DeBoer, Mueller, Scott and Griffin (Small Animal Dermatology), Thelma Gross and Julie Yager (dermatohistopathology) Linda Frank, Dunstan (alopecia and hair follicle biology). There are many more that I could list but these are the ones that have had the biggest impact on my increased knowledge in the last 20 years and without them our patients would be worse off. They deserve our thanks.

As well as increased understanding we need tools to work with. There are things we have now that we could not imagine being without. For many of these advances we have industry (pharmaceutical companies) to thank. Companies like Merial, Intervet-Schering Plough, Novartis, Pfizer, Hills, Virbac, Bayer, Dermcare, Troy, Fort Dodge, PAWs, Alanco, HESKA have brought us a range of new medications and diagnostic tools that we simply can not do ‘good medicine” without. Many of these medications will feature in our discussions. One group that require special mention are the safe and effective products for controlling that formidable adversary, the flea!

CONCLUSION

Availability of information, knowledge and collective clinical experience has come a long way forward since the 1981 PGF refresher that I have been referring to in these notes. In 20 to 30 years from now it is likely that what we present today will appear equally out of date. However, what will be presented over the next 3 days is the most current dermatology information distilled by clinically experience. I hope you enjoy the journey and appreciate that contribution made by some passionate veterinarians AND the companies that support our noble profession.

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NOTES:

Chapter 10

Anatomy and Pathology of the Ear

Linda J. Vogelnest
BVSc MACVSc FACVSc

Ear diseases are very common in small animal veterinary practice, particularly in the dog, with cases often presenting on a daily basis. Many acute cases are relatively simply managed, while other more chronic and/or severe cases may be poorly responsive or recurrent, causing a great degree of frustration to owners and veterinarians, and discomfort to patients. Having a good understanding of ear diseases will ultimately allow formulation of more effective short and long term management plans. A good understanding includes going back to the basics, and not only having a thorough knowledge of the anatomy and physiology of a normal ear, but also understanding the pathological changes that occur with ear disease, and how these may influence the course of disease.

Why are we talking about ear disease in dermatology?

No, it's not just because dermatologists like managing frustrating cases! Firstly, ear canals are lined by modified skin, which has many of the same structural components as for skin elsewhere on the body, including sweat glands, hair follicles, and an epithelial lining. As a result, many of the same principles that apply to skin disease elsewhere on the body also apply to diseases affecting the ear canals. Despite similarities, there are also some important differences between skin and ear canals, which must be appreciated in order to manage ear diseases as effectively as possible. Secondly, in addition to being lined by modified skin, ears are frequently affected by many of the same primary diseases that result in skin diseases. In particular hypersensitivities, including atopy and food adverse reactions, are very common underlying causes of ear disease, which may occur with or without concurrent skin signs. A range of other primary diseases that will often cause skin signs are also less commonly linked to ear disease, including hormonal, immune-mediated, and neoplastic diseases.

Basic anatomy with a tad of evolution!

The ear evolved as an organ of balance and hearing in vertebrates, and retains a similar and fascinatingly complex anatomical structure across vertebrate species including humans. The ear functions by collecting sound waves for transduction at multiple interfaces within the ear to ultimately produce neural messages for transmission to the brain. In mammals the ear consists of three regions: the external, middle, and inner ear. The most primitive part is the inner ear, present in all vertebrates, that consists of a membranous portion and a bony labyrinth. Amphibians and reptiles developed an additional chamber, the middle ear, formed by a tympanic cavity that is an extension of the pharynx, connecting to it via an auditory tube, and closed to the outside by a tympanic membrane. They also have a bony ossicle to transmit vibrations from the tympanic membrane across the air-filled tympanic cavity to the inner ear. In mammals two more ossicles are added, making a chain of three bones connecting to the inner ear, which are the smallest bones in the mammalian body. Lizards and birds have a rudimentary external ear, consisting of an auditory meatus and a short canal only, which may be protected externally by special scales or feathers. Only mammals, with the exception of some marine mammals (dolphins, whales, and some seals), have a well-defined external ear with a cartilaginous pinna, to enhance the collection of sound.[1-3]

Physiology: how do ears let us hear?

In all mammals hearing begins with the external ear collecting and directing sound waves to the tympanic membrane (ear drum), which is a taut thin membrane separating the external from the middle ear. When sound waves reach the tympanic membrane they cause it to vibrate. These vibrations are then transmitted via the three bony ossicles to the fluid-filled inner ear, where fluid movement is registered by surface projections (stereocilia) on specialised cells that lie within two main inner ear structures: the cochlea and semicircular canals. These specialised cells then release neurotransmitters that stimulate nerve endings of the cochlear and vestibular nerves, responsible for hearing and balance respectively. Finally nerve impulses are transmitted to the brain for interpretation, and we register sound. The type and intensity of sound influence the tympanic membrane vibrations, the movement of fluid in the inner ear, and ultimately the end neurotransmitter release, allowing us to register variations in sound. [1-5]

Detailed ear anatomy, including variations across species: is a cat ear just a small dog ear, and are they different to human ears? Can this help us with understanding disease?

1. EXTERNAL EAR

The external ear consists of the pinna and the external ear canal (also called the auditory canal or external auditory meatus). Both the pinnae and canals are composed of elastic cartilage which is covered by skin. The major portion, the auricular cartilage, is a continuous thin sheet that forms the flat pinnal surface distally and rolls into a thicker tube or funnel proximally to form the outer portion of the external ear canal, leading into the middle ear.[2-7]

The Pinna derives its *size and shape* largely from of the auricular cartilage. Pinnae are relatively small, erect and upright in the cat, uniform and flattened against the head in people, and very variable in the dog, where three general pinnal carriages are recognised: upright/erect/tipped, semi-erect/semi-pricked/bent, and long/lop-eared.[2,3,6,7] The less erect canine forms may reduce ventilation and increase local humidity, increasing susceptibility to external ear canal disease.[8] In the dog and cat an additional smaller scutiform cartilage lies medial to the auricular cartilage and within associated muscles at the base of the ear, firmly attaching the pinna to the head.[9] Movement of the canine pinna is controlled by 19 muscles, all innervated by branches of the facial nerve, allowing rotation on its vertical axis to facilitate picking up sound waves.[6-9]

At the entrance of the external ear canal there are a number of *cartilaginous folds* (gyri and sulci). In dogs and cats the most prominent of these is a raised central transverse ridge on the medial pinnal wall, above the ear canal entrance, called the anthelix. Another ridge, the tragus, is an irregular quadrangular plate of cartilage that forms the lateral wall of the initial portion of the ear canal. The pretragic incisure is a cartilage fold adjacent to the tragus, that is useful clinically as an easy site to guide entry of the cone for otoscopic examination.[2, 7] In contrast to dogs and cats, the entrance to the ear canal in humans has relatively small cartilaginous folds, resulting in a more open canal entrance with greater ventilation.[3]

The pinna is generously *vascularised* by branches of the external carotid artery which pass along its convex (outer) surface, wrap around the pinnal margins (helices), and penetrate through numerous small perforations to also supply its concave (inner) surface.[2,3,9] Traumatic injury to the pinna or violent shaking of the head may result in fracture of the delicate auricular cartilage and associated haemorrhage producing aural haematomas.[2,3] Aural haematomas are particularly common in the dog, most frequently associated with irritation from concurrent otitis externa, and can be extensive, filling the entire concave pinnal surface.[2,8,9]

Important point: Don't forget to check the ear canal when managing an aural haematoma: there is often concurrent ear canal disease, requiring active intervention for efficient and sustained resolution.

The External Ear Canal extends from the ear canal opening to the tympanic membrane. In humans the entire canal is horizontal, ~2.5cm long, and surrounded by cartilage (outer 1/3rd) and bone (inner 2/3rd). At the medial end there is a recess in which wax, debris, or foreign bodies may lodge.[3] In contrast, the feline and canine external ear canal is predominantly encased in cartilage, and in the dog varies from ~5-10cm in length and ~4-10mm in diameter, varying with breed, being particularly narrow in the Sharpei.[1,2,6-9]

The external canal is divided into an *outer vertical* portion, ~2.5cm long, formed by the rolled auricular cartilage, and an *inner horizontal* portion that leads to the tympanic membrane. The vertical canal runs ventrally and slightly rostrally until curving ~75° medially into the horizontal canal.[7,9,10] The horizontal canal is given its shape and support by the annular cartilage, which attaches to the auricular cartilage and to the osseous opening into the bony middle ear cavity.[7,10] This osseous external acoustic meatus is a short tube in the dog, a fine bony rim in the cat, and a long bony tube in humans and some other mammals including the rabbit.[3,9,11] The arrangement of separate rings of cartilage in dogs gives the external ear canal flexibility, which facilitates otoscopic evaluation despite the angled canal.[7]

Important point: When performing an otoscopic examination in dogs, pull up firmly on the pinna and gently manoeuvre the otoscopic cone to straighten the ear canal and enhance clear visualisation of canal structures, including the tympanic membrane at the base.

Histology: Boring You May Say? Regardless, It's Important!

For many vet practitioners histology is somewhat of a vague memory from uni days that often doesn't seem all that relevant to practice, other than knowing how to interpret results when they come back from the pathologist. When it comes to ear disease, knowledge of normal histology and the common changes that occur with disease, especially with chronicity, is very relevant to managing chronic and/or severe cases.

The pinna and external ear canal are covered with smooth skin that contains variable numbers of hair follicles, and numbers and types of sweat glands. In ***dogs*** and ***cats*** both sides of the *pinnal skin* have *ceruminous glands* (modified epitrichial sweat glands), and *sebaceous glands*.[2,12] There are often tufts of *hair* on the lateral side of the ear canal entrance where inner pinnal skin becomes confluent with facial skin.[7,12] In ***human*** pinnal skin *etrichial (eccrine) sweat glands*, which are absent in dogs and cats, predominate, *ceruminous glands* are sparse, and *hairs* are very fine and sparse.[4,5]

In ***humans***, the outer *cartilaginous canal* contains *hairs* and *ceruminous glands*, but no etrichial (eccrine) sweat glands. The *inner bony canal* has very thin lining skin that lacks rete ridges and is adherent and sensitive, with only a few small *hairs* and *sebaceous glands*.[3,4]

In the ***canine*** external ear canal both the *vertical and horizontal portions* are lined by flat epidermis similar to the pinnae, and have relatively sparse *hair* follicles, and *sebaceous* and *ceruminous glands* that are much more numerous and obvious in the distal (outer) third of the canal.[2,10,12] The density of ceruminous glands and hair follicles is breed dependent unlike that of sebaceous glands. In normal canine ears sebaceous glands are usually very prominent and actively secreting. *Hair follicles* are fewer and smaller than in other areas of normal skin. A tuft of hair may be present in some dogs in front of the tympanic membrane.[7,10] Long-haired breeds, including the labrador, cocker spaniel, english springer spaniel, airedale, and old english sheepdog have more follicles and glands than short-haired breeds such as greyhounds and cross-breeds.[9,10] In contrast, the ***feline*** external ear canal is largely devoid of hairs.[9]

The ***ceruminous glands*** closely resemble epitrichial (apocrine) glands, which are widely distributed in canine skin and predominantly located in axillae and pubic areas in human skin. They are numerous in the human external ear canal, with an estimated 1000-2000 ceruminous glands in the average ear,[4] however are more difficult to detect in healthy canine ears.[12] In both species they occur as deep coiled tubes situated below the sebaceous glands and just superficial to the cartilage layer. They consist of 2 layers of cells: an inner secretory layer of cuboidal cells with abundant eosinophilic cytoplasm (which can pinch off to lie loosely within the gland) and yellowish-brown acid fast pigment granules; and an outer myoepithelial cell layer encircling the secretory cells, consisting of flattened cells with spindle-shaped nuclei and eosinophilic cytoplasm.[4,12] A layer of collagen is often present external to the myoepithelial layer, separating the glands from adjacent tissue. The ceruminous glands open via ducts, invariably directly onto the skin surface in dogs,[12] although mostly into the luminal part of the hair follicle in humans.[4] The ceruminous gland ducts consist of 2 layers of cuboidal cells, and no myoepithelial cells or external fibrous layer, and may develop multiple layers and form keratinising epidermoid cells more peripherally.[4]

From a surgical perspective, very important structures to identify in the external ear include ***branches of the auricular arteries*** (numerous on the lateral aspect of the ear canal), the ***facial nerve*** (arises at the level of the skull caudally and ventrally to the external auditory meatus, wrapping around the ventral surface of the ear canal to distribute across the face), and the ***retroglenoid vein*** (exits from the retroglenoid foramen, craniodorsal to the auditory meatus, and can result in severe, life-threatening haemorrhage).[10]

In the normal external ear canal, exfoliating cells and glandular secretions from sebaceous and ceruminous glands form ***wax (cerumen)*** which protects the canal by immobilising foreign objects and keeping the tympanic membrane moist and pliable.[2,6] Actively secreting sebaceous and ceruminous glands contain large amounts of lipids, glycogen and both acid and alkaline phosphatases. Ceruminous gland secretions also contain mucopolysaccharides, and are acidic in comparison to the more neutral secretions from sebaceous glands.[12] Immunoglobulin (IgG and smaller amounts of IgA and IgM) have also been identified in canine cerumen.[5,12] In normal ears, epithelial cell migration, that commences at the tympanic membrane and moves peripherally out of the ear canal, clears out the epithelial cells and cerumen and any trapped dirt and debris.[5,9]

Diseases of the External Ear

The vast majority of ear disease in dogs involves the external ear, with either or both the pinnae and ear canal affected.

a) ***Pinnal*** disease is relatively common. Pinnal ***skin*** is affected by a wide range of skin diseases, including hypersensitivities, immune-mediated diseases (vasculitis; pemphigus foliaceus), and infectious causes (otodectes mites) which may involve other body regions also or be restricted to the pinnae.[3,5,8] Diseases of pinnal ***cartilage*** also occur, including auricular chondritis recognised in cats, and relapsing polychondritis in humans.[4,5]

b) ***Otitis externa*** (OE), defined as inflammation of the external ear canal, is extremely common in the dog, estimated to occur in 15-20% dogs at least once in their lives,[5,9] and is comparatively less common in the cat (4%) and in humans.[3,5,13] The more poorly ventilated canals of dogs with pendulous pinnae and/or relatively hairy canals, and the greater physical length of many canine external ear canals are proposed as important predisposing factors to disease. In humans it is suggested that a narrow or tortuous external canal is associated with an increased susceptibility to OE.[3]

A number of similar **histopathological changes** are associated with OE across all species. ***Hyperplasia*** of the epidermis (hyperkeratosis and acanthosis) is a frequent early change. In dogs the epithelium increases to 5-6 times normal thickness, forming numerous distinct rete ridges extending into the dermis. There is also often ***hyperkeratinisation of the hair follicles***, and in early stages ***hyperplasia of sebaceous glands*** with obvious dilation of ducts. In most cases there are numerous ***aggregates of inflammatory cells*** in the deeper layers of the epithelium and dermis (lymphocytes, plasma cells, polymorphs and macrophages), particularly surrounding ceruminous glands. ***Dermal vasodilation and oedema*** are also common, and frequently a large amount of pigment, presumably produced by the ceruminous glands is present in the superficial dermis.[10,12-14] In more chronic cases hyperplasia is even more marked, resulting in constriction of the lumen of the external ear canal, and ***ceruminal gland hyperplasia and cystic dilation of glands and ducts*** become particularly striking in both dogs and cats, and can almost completely displace the sebaceous glands.[12,13] The normally thin and straight ceruminous glands, difficult to distinguish in healthy ears, become filled with eosinophilic homogenous material and thrown into numerous twisted convolutions, which give the appearance of a large number of glands when cut in cross-section.[12,13] Papillary proliferation of the cyst and duct epithelium, and of the myoepithelium can occur. Polymorphs and some lymphocytes may occur in the secretions within their lumina, and in cats circumscribed granulomatous inflammation can occur.[12,15] ***Hyperaemia*** and ***areas of ulceration*** of the lining epithelium may occur, particularly with gram negative bacterial involvement, and proliferation of fibrous tissue may also occur in the dermis; all adding to canal occlusion.[12,14] ***Diffuse polypoid lesions*** or sometimes localised ***inflammatory polyps***, presenting as pedunculated smooth masses covered with squamous non-keratinising epithelium or columnar epithelium (sometimes ciliated) can occur.[13] Polyps are well-recognised in cats, where they can arise from the pharyngeal mucosa, the auditory tube, or the middle ear, and may be congenital, or secondary to viral or bacterial infections.[5] In some dogs ***ossification*** of the external ear canal occurs with chronicity, which may extend to also involve the cartilage.[13] In end-stage ears undergoing surgical ablation, Cocker spaniels were found to have a strong predisposition for proliferative ceruminous gland hyperplasia and ectasia, while fibrosis with less prominent glandular activity was the predominate pattern for other breeds.[16]

OE often results in ***altered and increased ear secretions*** which are associated with *increased ceruminal* gland and *decreased sebaceous* gland activity, the inflammatory reaction, and with pyogenic bacteria or yeasts where present. It has recently been proposed that cerumen may be a good growth medium for certain bacteria, and that the copious secretions accumulating in chronic inflammation may enhance bacterial survial.[12]

What does all this mean? In OE there are a number of physical, chemical, and immunological changes in the microanatomy of the canals that occur associated with inflammation from chronic disease. The end result is an occluded canal with excessive desquamating material, glandular secretions, heat, and reduced ventilation that is perfect for microbial growth. **The ear becomes an incubator!** These inflammatory changes alone, irrespective of the underlying primary cause of ear disease, and also irrespective of any secondary bacterial or yeast infections, must be addressed for successful disease management.

Crucial point: Bacteria and yeast are sometimes the bad guys in OE, but generally only over time as we actively select for more resistant populations. More often the major enemy are the inflammatory changes, which will take time to reverse and must have targeted treatment. Thus when dealing with chronic ear disease, returning the ear canal microanatomy to normal is the first and often major challenge, with removal of established bacterial and/or yeast infections an initial part of this. Preventing disease reoccurrence by addressing the underlying primary disease is the second challenge, which will often be less difficult to achieve.

2. TYMPANIC MEMBRANE

The tympanic membrane (TM) or “ear drum” is a thin, slightly opaque membrane separating the horizontal portion of the external ear canal from the tympanic cavity of the middle ear. It is a natural barrier that helps to keep the delicate structures within the middle and inner ear safe. Being a barrier, its protective effects will work both ways; tending to keep infections that start in the external ear out, but also tending to keep those that start in the middle ear in. In the dog, OE is the most common initial disease, while in the cat and human middle ear disease often comes first.

The TM has a concave shape that gives a well-defined light reflex, making it readily visualised in normal ears on otoscopic examination. When attempting to visualise the TM via otoscopic examination, you will need to have a non-moving patient, minimal ear canal wax/discharge, and pull up on the pinna gently but firmly to straighten the bend in the ear canal at the junction of the vertical and horizontal canals.

Important point: Being unable to visualise the TM in an inflamed ear using an otoscope does not always mean it is absent; the canal may be too narrowed to get the scope deep enough, or thickened and folded epithelial lining may be obscuring it. Gently flushing the ear canal with saline under GA to remove all discharge, and checking the level of the TM in the other normal or less affected ear if possible can help with TM evaluation. Where available, video auroscope examination will allow much more accurate evaluation, however prior systemic anti-inflammatory therapy may be important in occluded canals.

The TM is oval to circular in shape, located at a 45°angle to the central axis of the horizontal canal in dogs, and divided into two visually distinct portions: the small (~¼) upper pars flaccida and larger (~¾'s) lower pars tensa.[1-3,9,12] In the dog, otoscopic examination will usually reveal a portion of the pars flaccida and the posterior quadrant of the pars tensa.[12] The ***pars flaccida*** is a small triangular portion located dorsorostrally in the membrane that visually looks more similar to the lining skin on the adjacent horizontal canal. It appears opaque, pink, or white, and contains small branching blood vessels.[2,3,7,12] The pars flaccida or structures in this region appear prominent and bulging in some dogs, which may result from oedematous tissue on the dorsal wall of the horizontal canal adjacent to the tympanic membrane in inflamed ears, but has also been recognised in normal ears.[14,17] A study in four dogs found no histological differences between bulging and non-bulging pars flaccida, concluding differences in middle ear pressure may be important to this recognised variation in appearance.[17]

The ***pars tensa*** forms the bulk of the membrane and is thin, tough and glistening, usually pearl-grey and translucent, although may have opaque radiating strands. The external surface is concave and at the point of greatest depth of the concavity, near the centre of the membrane, the first of the middle ear bones, the ***malleus*** attaches. As the normal pars tensa is partially transparent, the area of attachment to the malleus bone (stria mallearis) is normally visible as a central light-coloured streak, and is the area where many of the blood vessels and nerves occur.[2,3,6,9,12] The pars tensa is thinnest in the center and thicker on the periphery where it is attached firmly to the surrounding bone by a fibrocartilaginous ring (annulus fibrocartilaginous) which attaches to the osseous external acoustic meatus by fibrous tissue.[7,9]

Important point: Myringotomy incisions should be made in the caudoventral portion of the pars tensa.[7] Don't consider performing a myringotomy without a full appreciation of normal anatomy at this site!

Histology: Normal Microanatomy!

The TM consists of four histological layers: the external epidermal, innermost mucosal, and two layers of intervening connective tissue. The ***external epidermal layer*** is continuous with the epithelial lining of the distal portion of the external ear canal, and is thin, lacks hair follicles and sweat glands, and consists of a flat basal layer and a superficial layer only a few cells thick. It is thicker in the pars flaccida (up to 10 layers) than in the pars tensa (7-8 layers).[4,9] The ***middle connective tissue layer*** consists of a thick zone of loose collagen and elastic fibres in the pars flaccida, and a unique finely structured collagenous double layer in the pars tensa, with an outer layer of fibres radiating toward the annulus fibrocartilaginous from the center of the eardrum, and an inner layer of fibres that are circular.[4,9] The periosteal connective tissue of the manubrium of the malleus is within these connective tissue layers, and has a hook in the dog that points rostrally. The ***inner mucosal layer*** is similar in both the pars flaccida and the pars tensa, and rests on a lamina propria of collagenous fibres with a fine network of capillaries. It is composed of a single layer of respiratory epithelium that lacks the goblet cells and cilia characteristic of respiratory epithelium, and varies gradually from columnar at the periphery, to cuboidal, and finally to squamous at the center. This layer is continuous with the mucous membrane type of respiratory epithelium covering the middle ear cavity, auditory tube, and the nasal cavity (see below). It reflects over the surface of the manubrium of the malleus.[4,9] In addition, the pars flaccida contains an intricate external and internal vascular plexus of capillaries, arteries, veins and nerves.[17]

The concave shape of the normal TM on otoscopic examination is due to tension on the internal surface where the malleus attaches. Epithelial cell proliferation in the TM originates from the point of greatest depression (the umbo) with new cells radiating outward, forcing new keratinised cells to migrate to the periphery and out the ear canal rather than thickening the TM.[2] This epithelial cell migration allows clearing of the accumulated desquamating keratinised cells and glandular secretions in the external ear canal. Failure of epithelial movement can occur due to a number of mechanisms, resulting in accumulation of wax and cell debris. In older animals and humans it results from a slowing of cell turn over. In chronic inflammation it can result from damage to the external epithelial layer of the TM.[18] Poor epithelial cell migration may result in excessive scaling along the ear canal surface, or more often either soft plugs or hard ceruminoliths, which accumulate at the base near the TM, often attached to hairs.

Disease of the TM

Myringitis (tympanic membrane inflammation) occurs frequently associated with otitis media. Changes include epithelial hyperplasia, focal epithelial ulcerations, and oedema and hyperaemia of the connective tissue layers. Granulation tissue formation can produce polypoid extensions into the middle ear, which may adhere to the middle ear mucosa.[14] Visually there is a loss of lustre, increasing opacity, and development of a grey or grey-white appearance. Small vessels on the periphery and adjacent to the manubrium of the malleus may appear injected. Later the pars tensa may become wrinkled and develop dark necrotic clefts, heralding imminent rupture.

Severe diseases originating in either the external canal or middle ear may result in TM rupture, due to pressure and/or weakening from inflammation and disease. In humans rupture mostly occurs from ischaemic necrosis at a focal point due to pressure in the middle ear, usually in the pars tensa.[3,4,12]

Important point: Rupture of the TM is not as disastrous and sometimes thought: it is typically a reflection of the severity of disease, which is more influential on ultimate outcome than the state of the TM itself. Repair will often occur quickly with good disease management.

A normal human TM has been shown to heal in 21-35 days after experimental complete destruction,[7] and in humans, rabbits, rats, and guinea-pigs perforations will heal rapidly and spontaneously, even in the presence of otitis media, although permanent fistulae may sometimes form.[14]

3. MIDDLE EAR

The middle ear is often involved in feline and human ear disease, and most typically concurrent with OE in some cases of canine ear disease. Middle ear disease can cause considerable pain and debility, and complicate disease management of OE when concurrent. It thus requires quick recognition and aggressive treatment, backed by a good understanding of disease principles, to hasten resolution.

The middle ear (tympanic cavity/tympanum) is a hollow air-filled bony chamber within the petrous temporal bone that contains the three ***ear ossicles***, with their associated muscles and ligaments, and the ***opening of the auditory (Eustachian) tube***. It is separated from the external ear by the tympanic membrane laterally, connected to the pharynx via the auditory tube rostrally, and contains two openings dorsomedially into the inner ear, deeper in the petrous temporal bone: the ***vestibular (oval) and the cochlear (round) windows***, both covered by membranes.[1-3,8,9,12,19] The vestibular window is ~ 18-20 times smaller than the tympanic membrane, which contributes significantly to sound amplification.[9]

The middle ear can be divided into three parts: dorsal, middle and ventral areas. The smallest ***dorsal section*** (*epitympanic recess or "attic"*) contains two of the three middle ear bones, the malleus (which extends ventrally into the middle section where it attaches to the tympanic membrane) and the incus (which is suspended between the malleus and the third bone, the stapes).[2,5,9,12,19] The ***middle section*** of the tympanic cavity (*tympanic cavity proper*) is adjacent to the tympanic membrane, and contains the opening to the auditory tube ventrally and the cochlear and vestibular windows dorsomedially. The stapes lies in the tympanic cavity, and attaches to the vestibular window. The ***ventral and largest portion*** of the tympanic cavity (*tympanic bulla*) is important to sound resonance, but also acts as a reservoir to trap debris and toxins in otitis media.[5].[2] The ***auditory tube*** is responsible for the aeration of the middle ear, which is important to reduce the acoustic impedance that would occur if sound waves in air were to be applied directly to the fluids within the inner ear. Without this impedance matching, 99% of the sound energy would simply be reflected at the air/fluid interface.[3] Both left and right auditory tubes have separate openings into the nasopharynx, dorsolaterally, approximately mid-way along the soft palate, and are surrounded by cartilage towards the nasopharynx and bone near the bulla. Contraction of two small palatine muscles, innervated by branches of the trigeminal and facial nerves, occurs during swallowing, and keeps the auditory tube patent. There are also two small ***striated muscles*** within the middle ear, the *stapedius* connected to the stapes, and the *tensor tympani* connected to the malleus that enhance low-frequency and high frequency sounds respectively. It is also thought that these muscles dampen the movement of their bones of attachment to limit excessive movement and protect against loud or repetitive sounds damaging the sensitive inner ear structures.[2,4] The ***facial nerve*** with its parasympathetic branches that innervate the tear glands as well as the sympathetic nerve is closely associated with the middle ear, resulting in neurological deficits associated with otitis media.[8]

Species Variation

In the dog the tympanic cavity is one large pear-shaped compartment, approximately 8-10mm in diameter, with a dorsal recess, [2,8,9,12] while in humans it is approximately 15mm high x 15mm anterio-posteriorly, although only 2mm deep in parts. The wall is very thin and easy to remove in dogs, and the cavity is more flattened in some breeds, including the Cavalier King Charles Spaniel.[20] In the cat the tympanic cavity is elongated,[11] and divided by a incomplete bony septum into two separate tympanic cavities: a small dorsolateral compartment containing the auditory ossicles, the opening of the auditory tube, and the tympanic membrane; and the larger ventromedial air-filled tympanic bulla compartment. The two compartments communicate via a small passage located dorsally near the cochlear window.[8,9,20] The bony septum between the two compartments needs perforating to establish good drainage of the tympanic cavity surgically, although the adjacent post-ganglionic sympathetic nerves are easily damaged during this procedure.[9]

The auditory tube is 5-15mm long and 1-3mm diameter in dogs,[1] and 32-38mm long in humans, with the pharyngeal cartilaginous part somewhat longer than the tympanic or osseous part.[3] The narrowest portion, with a luminal diameter of 1mm, is the tubal isthmus, which lies between the osseous and cartilaginous parts. The lumen of the pharyngeal part is practically only a fissure, which is mostly closed.[19]

In humans a relatively narrow passage (aditus) leads from the attic into a larger, irregular cavity, the mastoid antrum, which extends ventrally and caudally into the mastoid cell system. This unique system contains mastoid air cells, a network of mucosa-lined intercommunicating spaces of varying size and shape. They have a skeletal framework, with a thin bony trabeculum of lamellar bone, and form a honeycomb within the temporal bone, acting as a reservoir of air to limit pressure changes within the middle ear. The extent of pneumatisation is very variable and determines the size of the antrum. A lesser degree of pneumatisation may be associated with a hereditary small cellular system, and/or frequent episodes of acute infection, especially during childhood.[3,4,19]

Histology: Normal Microanatomy

The auditory tubes and the adjacent middle areas of the tympanic cavity are lined by a very thin strongly ***modified respiratory mucosa*** with small numbers of ciliated and secretory epithelial cells, resembling that found in the nose, paranasal sinuses, and lower airways, and also a basal membrane and lamina propria.[12,14,19] This pseudostratified epithelium has four types of cells of variable height and shape with nuclei at different levels. All cells extend down to the underlying basement membrane: high cylindrical ciliated cells, mucous secreting goblet cells, supporting cells, and round undifferentiated basal cells, thought to possess regenerative ability, which are the only ones not in contact with the luminal surface of the epithelium.

The ***goblet cells*** and ciliated cells are the most important and most characteristic cells of the respiratory mucosa, responsible for cleansing of the respiratory tract surface by the mechanism of a moving mucous stream. The nucleus of a goblet cell lies in the basal part of the cell, with the organelles and secretory granula toward the luminal surface. The granula are emptied onto the surface through a small opening. Goblet cells take on different shapes depending on the thickness of the epithelium, the degree of maturity, and the secretory phase of the cells, being tall and slim in areas where pseudostratified cylindrical epithelium is high, with a stalk-like contact with the basement membrane. The secretory cycle of the goblet cells comprises three phases: formation, accumulation of mucin (enlarging the cell), and excretion of mucin (reducing the cell size again). They generally take 14 days to develop, proposed from basal cells, but in pathologic conditions increased density occurs after 3 days.[19] Goblet cells proliferate in any part of the respiratory epithelium when irritated by infective, gaseous or vaporous agents.[4,19] The are distributed irregularly, in heaps, pairs, or singly.[19]

Ciliated cells are interspersed amongst the goblet cells, decreasing in number from anterior to posterior in the middle ear, corresponding with the changes in height and character of the epithelium. The largest numbers occur in the auditory tube and the middle ear cavity adjacent to it. Mucous from the goblet cells and submucous glands lies on the surface of the periciliary layer, most frequently in the form of small droplets or plaques, and rarely as a continuous layer.

In the normal middle ear the mechanism of the ***mucociliary clearing*** is more complicated and irregular than in the upper and lower airways. With considerably less need for clearance in the middle ear and no great need for transport of mucous, there is an extremely low density of mucous-producing goblet cells and no mucous-producing glands in the normal mucosa. The auditory tube and anterior tympanic cavity are the only places with a continuous layer of cilia (>80% cells are ciliated) that is capable of clearance in a degree comparable with the nose and sinuses. More posteriorly and medially in the middle ear 11-50% cells are ciliated, and in the attic only 1-10%. In the auditory tube every ciliated cell carries from 40-60 cilia, anteriorly in the nose from 50-100 cilia, and in the trachea about 200. Cilia are 2um in diameter, and 5um long in respiratory passages compared to 7um in the auditory tube. Goblet cell density in the auditory tube changes through childhood, increasing in the pharyngeal part, however does not change with age in the middle ear.[4,19]

In contrast, the auditory tubes and adjacent areas, most of the ventral, dorsal and posterior portions of the tympanic cavity (including the auditory ossicles, inner surface of the tympanic membrane, membranes over the cochlear (round) and vestibular (oval) windows), and the mastoid air cells in humans, are lined by a thin layer of ***simple cuboidal to squamous epithelium***.[4,14] The epithelium is not uniform in all areas, and the transition from one kind to another is gradual. Focal zones of ciliated pseudostratified epithelium occur. Stratified (multilayered) squamous epithelium is not a feature of the normal ear, but may be found in patches (squamous metaplasia) or as a cystic formation (cholesteatoma) in the abnormal middle ear. Gland formation is also not a feature of the normal middle ear mucosa and is induced by inflammatory change. The normal middle ear mucosa contains ***very few immunocompetent cells*** and is unable to produce as effective a local immune response as other types of mucosa. It does have a latent ability to perform local synthesis of immunoglobulin, and production can increase when density of secretory cells increases in pathologic conditions.[4,19]

Middle Ear Disease

Otitis media (OM) refers to inflammation of the mucous membrane of any part or whole of the middle ear: the auditory tube, tympanic cavity, attic, and mastoid antrum and air cells.

It is one of the most common of all diseases in ***humans***, particularly in young children, and is most frequently associated with primary viral respiratory tract infections, although secondary bacterial infections may be more responsible for clinical disease. Infection typically occurs via the auditory tube, with viruses possible agents for bacterial seeding in early phases of disease, although sometimes sole pathogens. ***Rhinoviruses***, and less commonly respiratory syncytial viruses have been cultured from the middle ear in humans with OM.[3,4] Dysfunction of the auditory tube appears to play a role, with early closure of the central lumen from oedema preventing normal middle ear aeration and drainage.[3,14] Other causes of OM in humans include acute bacterial tonsillitis, other viral infections (influenza, measles), and external trauma or pressure damage.[4] The external ear canal and pinna are rarely involved.[4]

In the ***dog*** OM is also common, however in contrast to humans, in the vast majority is an ***extension and complication of OE*** associated with tympanic membrane rupture.[5,12] Despite this, histological changes in canine OM are very similar to those in other species including humans where OM is mainly associated with respiratory tract infections.[14]

Similarly to humans, respiratory infection-linked OM is relatively common in the ***rabbit*** and ***cattle*** amongst other domestic mammals, with a variety of organisms implicated including *Pasteurella multocida* in both cattle and the rabbit, *Mycoplasma bovis* and *Corynebacterium* spp. in cattle, and respiratory rhinotracheitis or parainfluenza viruses.[11,14,21,22] Younger cattle, including yearlings and especially calves, are most commonly affected by OM.[22]

In the ***cat*** OM is reported less commonly, and most frequently associated with bacterial infection (middle-aged cats), inflammatory polyps (young cats), or neoplasia (older cats).[23] Inflammatory polyps are commonly associated with upper respiratory tract signs, which may develop secondary to physical obstruction from the polyp, however prior bacterial rhinitis or sinusitis are also implicated in their pathogenesis.[24] There is no apparent association of feline OM with respiratory viral infections despite their high prevalence, especially in younger cats. The potential origin of bacterial OM in middle-aged cats appears unevaluated, but may include extension of OE or complication or extension from bacterial or viral respiratory infections.[5]

Bacteria involved in acute OM in ***humans*** include *Streptococcus pneumoniae* and *Haemophilus influenzae* most commonly, with gram negatives more typical in chronic disease, including *Proteus* and *Pseudomonas* spp. and less commonly *Staphylococcus pyogenes* and beta-haemolytic *Streptococc*i.[4] In ***dogs*** *Staphylococcus intermedius*, and gram negatives: *Pseudomonas* spp., *Proteus* spp, *Escherichia coli*, and *Klebsiella* spp. are most commonly isolated. *Malassezia pachydermatis* is also a common cause of canine otitis externa, and may be involved in otitis media.[5]

Histopathology

Acute OM is characterised by severe ***hyperaemia*** and ***oedema*** of the mucosa of the middle ear and the tympanic membrane. Plasma may leave a deposit of ***fibrin*** within tissues. A ***fluid exudate*** within the middle ear cavity is frequently a prominent component of the inflammatory reaction, producing OM with effusion.[4] The exudate can vary from yellow and purulent, to dark brown and fluidy, and may contain hair, adnexal glands and/or inspissated debris (light dirty grey to brown-black) and/or foreign material (grass awns).[12,14] ***Mucous*** may be secreted by newly formed glands in the mucosa to contribute to the exudate. ***Inflammatory cells*** are mostly neutrophils, with histioctyes, lymphocytes, and plasma cells appearing with chronicity.[4,14] Organisms are rarely seen on histopathology.[4]

In more chronic OM the most characteristic feature is the presence of ***inflammatory granulation tissue***, consisting of *leukocytes* (lymphocytes, plasma cells, histioctyes), and granulation tissue (newly formed *capillaries* and *fibroblasts*).[4,14] Lymphoid follicles with germinal centres are reported in dogs.[14] The granulation tissue is often loose, vascular and oedematous, but may form dense mature connective tissue in some cases, occasionally containing spicules of bone.[14] It may also form ***aural polyps***, which in the middle ear are often covered by columnar epithelium, frequently ciliated, and have a core of chronic inflammatory granulation tissue.[4]

Sometimes groups of keratin squames with foreign body type giant cells predominate, especially in the presence of choleasteatoma of the middle ear, which is important in up to 50% of chronic OM cases in humans. ***Choleasteatomas*** are cysts within the middle ear cavity lined by squamous epithelium producing keratin lamellae, that can be congenital or primary (forming behind an intact tympanic membrane) or acquired (associated with perforation of the tympanic membrane). Grossly they appear as a pearly grey or yellow cyst-like structure in the middle ear cavity. The wall of the cyst can appear as a thin membrane.[4] Choleasteatomas are reported in some dogs with OM.[14]

Foreign body type giant cells and other chronic inflammatory cells may also surround ***cholesterol granulomas***: yellow nodules composed of cholesterol crystals which dissolve away to leave empty clefts in paraffin-embedded histological sections.

Cholesterol granulomas are typically found in the midst of haemorrhage in the middle ear mucosa.

Other chronic changes in human OM include ***fibrosis*** of the mastoid air cells (the bony walls are markedly thickened with patchy sclerosis), and ***tympanosclerosis*** (deposits of dense white tissue consisting of hyaline collagen with irregular deposits of calcium salts in the mucosa on the inner surface of the tympanic membrane and within the tympanic cavity).[4] Both acute and chronic OM in humans, dogs and cats is also characterised by ***epithelial hyperplasia*** and similarly to inflammation in respiratory epithelium, undergoes reversion to a more secretory-type epithelium, changing from squamous or cuboidal to pseudostratified columnar.[4,14] ***Goblet cells increase*** with chronic OM to similar numbers as found in respiratory tract epithelium, and stain with PAS-Alcain blue as oval to round sharply demarcated blue structures on a pale background.[4]

Secretory otitis media (glue ear) is a form of chronic OM in humans in which the number of secretory cells and glands in the middle ear increases substantially.[14] Gland-like structures, sometimes progressing to cysts, are also recognised in chronic OM in dogs, containing little free glycoprotein, few glycoprotein-secreting cells, and sometimes cholesterol clefts.[14] Free keratin squames, often surrounded by a severe inflammatory cell reaction, can also be present within the middle ear cavity.[14] In addition to epithelial proliferation in chronic OM, the internal bony tympanic cavity walls can produce new bone, which is woven in early stages and lamellar later, or undergo bone remodelling.[4,14]

4. INNER EAR

The inner ear lies carefully protected within the bones of the skull, and is a complex structure consisting of an ***osseous labyrinth*** (series of canals in the petrous temporal bone which surround membranous portions called ducts). It lies dorsomedially to the tympanic bulla portion of the temporal bone, connecting to the tympanic cavity of the middle ear through the vestibular window.

The inner ear consists of three parts; the first part, the ***cochlea region***, is a spiralling tube around a central bony cavity (the modiolus) in which the cochlear nerve lies. This tube spirals 3 times in the cat and 3.25 times in the dog, and contains three longitudinal compartments (two osseous and one membranous) formed by two membranes that run the length of the cochlear. The ***osseous canals*** and ***membranous ducts*** contain fluid that differs in ionic composition: perilymph (similar to cerebrospinal fluid) in the canals, and endolymph (a clear dialysate of blood) in the ducts.

Within the cochlear, the ***vestibular membrane*** and the ***basilar membranes*** (scala)

divide the canals and ducts. The cells lining the basilar membrane (spiral organ/organ of Corti) are largely responsible for the transduction of sound, and consist of ***specialised hair cells***, each with numerous ***stereocilia*** projecting from their apices that lie within the endolymph-filled membranous cochlear duct. The tips of the tallest cilia are embedded in the tectorial membrane, a gel-like substance secreted from interdental cells located where the vestibular and basilar membranes meet. When tympanic membrane vibrations are transmitted to the inner ear structures, movement of the endolymph results in *bending of the stereocilia*, which produces a *voltage fluctuation* within the hair cells: movement in one direction produces depolarisation and in the other direction hyperpolarisation. On depolarisation a ***neurotransmitter*** is released from the base of the hair cell, which is taken up by axon neurons which feed to the cochlear nerve. The basilar membrane is narrow and rigid closer to the middle ear, where is it more responsive to high-frequency sounds, and broad and flexible at its end deep within the inner ear where it is responsive to low-frequency sounds.

The other two parts of the inner ear are important to balance, and consist of the ***vestibule*** which contains the ***otolith organ*** (saccule and utricle), and the ***semicircular canals***: posterior, superior and horizontal. Within the semicircular ducts, positioned at right angles to one another, movement of endolymph affects another group of specialised hair cells, similarly resulting in stimulation of the vestibular nerve. [1-3,9,12] Otitis interna is relatively uncommon in humans, and rarely reported in dogs and cats, and is most typically associated with OM. Although hearing deficits occur, clinical signs are typically due to upset of equilibrium and balance. [1-3,9,12]

CONCLUSION

Otitis externa is particularly common in the dog, and unique anatomical factors including long external canals, hairy folded canal entrances, and pendulous hairy pinnae likely predispose to disease. The relative importance of other factors including the incidence of common underlying diseases such as atopic dermatitis is unclear. Otitis externa is less problematic in humans and cats, although does occur.

Otitis media is problematic across species, and although it is most prevalent as an extension and important complication of otitis externa in dogs, it is interesting to compare to disease in humans and other domestic mammals where there is an association with respiratory viral infections and occurrence is largely independent of otitis externa. There appear to be no obvious anatomical differences to explain this contrast in disease pathogenesis across species. The higher frequency of disease in younger humans and cattle raises the possibility that anatomical size of the auditory canal, important to middle ear drainage, may be one important predisposing factor. The prevalence of primary underlying diseases may be more relevant to the pathogenesis of otitis media than anatomical differences. This theory is supported by a low prevalence of respiratory viral infections associated with prominent airway secretions in the dog, contrasting to a high prevalence of exudative respiratory viral infections in humans, rabbits and cattle. Conversely, the relative rarity of OM in young cats, where exudative respiratory viral infections are common, suggests there may be some protective mechanism against OM in cats.

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Chapter 11

Pathogenesis, Diagnosis and Principles of Management of Otitis Externa (Part 1 & 2)

Greg Burton FACVSc (Dermatology)

DEFINITIONS

- Otitis externa means inflammation of the external auditory canal (not necessarily infection).
- Infectious otitis externa means otitis complicated by bacterial and/or fungal overgrowth.
- Otitis media means inflammation of the tympanic cavity.
- Relapsing infection is the same infection returning shortly after therapy has ceased and indicates the infection never fully resolved
- Recurrent infection means that there was total resolution of the infection followed some time later by a new infection within the ear canal. The new infection may or may not be with the same organisms as the original infection
- Infection, unless stated otherwise, implies surface bacterial or fungal overgrowth. Most ear infection are SURFACE overgrowth rather than invasive disease.

INTRODUCTION

When reading the literature on the pathogenesis of otitis externa invariable the discussion turns to a familiar classification of predisposing factors (such as conformational problems that increase the risk of otitis externa without directly inducing the inflammation), primary causes (such as otodectes and atopic dermatitis that can directly trigger inflammation of the ear canal), secondary causes (such as bacterial and yeast overgrowth) and perpetuating causes (such as hyperplasia, stenosis and otitis media that maintain disease). In a clinical setting I do not find this classification system useful when trying to explain otitis to clients and as we are all very aware client understanding is pivotal to owner compliance. What I hope to do today is give you a clinically relevant overview of pathogenesis as this impacts on all our diagnostic and management decisions.

The canine external auditory canal (EAC), as we have just heard from Linda, is much longer than the human ear canal having both vertical and horizontal parts. The narrowest part of the EAC is the osseous canal (terminal portion in front of the tympanic membrane) where the EAC runs through a bony tunnel leading to the tympanic cavity. Many healthy ear canals are not sterile. Bacteria (*Staphylococcus spp, Streptococcus spp and less frequently Pseudomonas spp)* and yeast (*Malassezia spp*) can be found on both cytology and culture of normal ears. The epithelium lining the ear canal also desquamates similar to skin elsewhere on the body. These exfoliated cells admixed with glandular secretions from the sebaceous and apocrine glands lining the canal forms the "wax" or cerumen within the ear canal. The cerumen prevents desiccation in the ear canal by virtue of the lipid content (cholesterol, fatty acids, squalene, ceramides) and traps debris and slows down microbial growth. Microbial growth is inhibited by long chained fatty acids, lysozymes and pH of the canal. Wax does not accumulate in a normal ear canal due to "self cleaning" of the canal facilitated by the lateral migration of the epithelium (the skin grows out from the ear drum to the opening of the canal and acts like a conveyor belt to carry debris out). This action may be assisted by jaw movements that dislodge debris from the wall to facilitate expulsion. The epithelium itself is also critical to maintenance of a healthy ear via normal desquamation and innate and acquired immunological responses and tolerance to normal microbial flora.

Bacterial and yeast overgrowth of the external auditory canal (EAC) are common, especially in the canine. Microclimate change has been implicated but this is an over-simplication and studies looking at temperature and humidity levels in the EAC of OE ears and healthy ears did not show statistically different levels between the two groups. A more appropriate explanation for why dogs and cats get ear infections is a *failure of the normal homeostatic mechanisms of the ear canal!*

WHAT CAUSES NORMAL HOMEOSTATIC MECHANISMS IN THE EXTERNAL AUDITORY CANAL TO FAIL.

Anything that causes inflammation of the ear canals:

a) Parasites (Otodectes, Demodecosis, Scabies)
b) Foreign bodies (grass seeds)
c) Allergies (atopy, food adverse reaction)
d) Irritants (shampoos in the ear)
e) Other diseases involving the EAC (pemphigus foliaceous, juvenile cellulitis)

Anything that increases the moisture in the ear canals:

i. Swimming
ii. Over-use of ear cleaners
iii. High environmental humidity
iv. Breed factors (eg Cocker Spaniels, Shar Pei, Pugs, Cavaliers, Labradors, Springer Spaniels)
v. Stenosis of proximal canal
vi. Glandular hyperplasia (secondary to otitis)
vii. Idiopathic inflammatory hyperplastic otitis of Cocker Sp

Anything that interferes with "self cleaning":

i. Damage to the tympanic membrane
ii. Polyps, neoplasia or large foreign bodies
iii. Hyperplasia of the canal lining secondary to otitis.
iv. Congenital or acquired stenosis (eg narrowed osseous canal of Labradors, Cockers, Springer spaniels)
v. Sebaceous adenitis
vi. Keratinisation defects
vii. Endocrinopathy
viii. Idiopathic inflammatory hyperplastic otitis of the Cocker Sp
ix. Residues from ear medications

HOW DO WE APPROACH OTITIS EXTERNA

The symptoms of otitis externa (OE) are not difficult to recognise by owners (head shaking, pawing at the ear, hyperaesthesia or pain, erythema of the pinna +/- otic discharge, odour or head tilt). It is a common reason for dog owners to seek veterinary attention.

BASIC PRINCIPLES OF TREATMENT

a) Ask *WHY*? Unless the “trigger” for the OE is identified and controlled there is a high likelihood of recurrence

b) Fix the current problem (resolve the current infection/inflammation)

c) Prevent recurrence. Normalise the ear canal (resolve secondary sequelae and ensure normal self-cleaning) AND address the “ why “.

A) Ask Why

Otitis externa should always be considered a symptom rather than a diagnosis. Like every skin disease you need to take a good history. Always assess for historical evidence of triggering events eg swimming, being shampooed within the last 21 days, having ears pluck etc. History should also be directed at ruling in/out underlying diseases that can trigger OE, especially the hypersensitivity and parasitic diseases and to a lesser degree endocrinopathy. A full clinical examination should be performed prior to any aural examination. Look for evidence of hypersensitivity disease especially atopic dermatitis. Where swimming, foreign bodies and ear mites are ruled out, atopic dermatitis remains the most common cause of recurrent otitis in the dog. In cats I would evaluate carefully (historically and clinically) for evidence of respiratory disease. In my experience with cats, once parasitic causes are ruled out the most common cause of recurrent OE appears to be extension from otitis media.

If a ‘once off” controllable event is suggested as the trigger for the otitis externa then further investigation may not be needed. Where otitis externa is recurrent then every attempt to identify the trigger should be made, as it is futile to simply treat the otitis without resolving the trigger disease, failure is guaranteed. Where the otitis externa is a symptom of more generalised disease of the integument (atopy, food adverse reaction, pemphigus foliaceous) or systemic disease (hypothyroidism, hyper A), diagnosis relies on a systematic approach (signalment, history, general physical and dermatological examination, cytology and specific diagnostic testing).

B. Fixing the Current Problem

The client (and patient's) primary concern on presentation is resolving the discomfort (itch/pain) involved with the OE. Regardless of the initial trigger for the disease resolution requires addressing the acute issues of microbial overgrowth, inflammation +/- exudate accumulation within the canal.

i. Fixing the Current Problem: Direct Visualisation

Visualisation is essential for assessing the degree and type of exudate within the canal, severity of inflammation, the presence of ulceration or hyperplasia and integrity of the tympanic membrane. Visualisation may also allow direct identification of the trigger for the otitis eg *Otodectes*, polyps, foreign bodies. Painful ears require sedation or better still general anaesthesia. Never fight with a dog with a painful ear as this increases the risk of poor compliance if the dog becomes phobic about ear examination.

If exudate is occluding the EAC then mechanical cleaning is recommended. With inflammation in the EAC there is increased exfoliation, increased glandular secretions together with the inflammatory exudate (host response to bacterial antigens and/or exotoxins). Exudate prevents visualisation of the deep structures of the EAC, especially the tympanic membrane. Exudate also forms a physical barrier to antimicrobial penetration, may inactivate some antimicrobials (particularly gentamicin), often contains leucocytic proteases that contribute to inflammation, pain and microbial survival (in the case of *Pseudomonas spp*), may contribute to low O2 tension in the deep canal (favouring anaerobic overgrowth and inactivation of gentamicin) and contribute to maceration within the canal. In short, exudate is a major player is preventing resolution.

Cytology should be collected before and during cleaning. Collect samples from ALL levels of the ear canal, proximal, middle and deep. Remove

ALL exudate (David Robson will talk us through cleaning protocols later on today). Visualise the deep structures and identify the integrity of the tympanic membrane. Assess the ear canal for glandular and epidermal hyperplasia, stenosis due to oedema versus stenosis due to fibrosis, check for polyps and foreign bodies and tumours. Visualisation is greatly facilitated by general anaesthesia, thorough cleaning, video otoscopy and advanced imaging eg MRI. Visualisation and efficient cleaning can be difficult to achieve with standard hand held otoscopes.

Removal of the exudate reduces inflammation, improves the microclimate of the ear canal, allows better visualisation and hopefully assessment of the tympanic membrane. If provides a window of opportunity to fix the current problem by allowing access for appropriate medications to be instilled into the ear canal. It does not however fix the problem. Unless the correct medications are applied to the ear AND inflammation controlled, exudate will reform within the canal very rapidly.

ii. Fixing the Current Problem: Indirect Visualisation

The common otic preparations do not have registration for use inside the tympanic cavity thus where possible it is important to establish the integrity of the tympanic membrane. We will talk about the risks of ototoxicity a little later. What do you do when you cannot directly visualise whether the tympanic membrane is intact. Indirect assessment of the tympanic membrane includes;

a) Visualisation of air escaping from the tympanic cavity. The normal tympanic cavity is air filled. Where there is a breach in the tympanic membrane, fluid pressure when flushing the distal canal may displace air resulting in large air bubbles escaping from the deep canal.

b) Visualisation of fluid escaping from the tympanic cavity through the Eustachian tube. Colouring the irrigation fluid with an aqueous povodone iodine solution, to the intensity of weak tea, may help confirm the fluid exiting the nose is the same fluid being used to irrigate the EAC thus confirming a loss of integrity of the tympanic membrane.

c) Assessment of fluid retention in the tympanic cavity. Simply filling the EAC with a known volume of fluid, waiting 2 to 3 minutes and then aspirating the fluid and assessing the retained volume. A failure of fluid to be retained with the EAC would be confirmation of loss of integrity of the tympanic membrane. The converse is not true however as fluid can be retained within the tympanic cavity, not the EAC, where there is tissue within the tympanic cavity or occlusion of the Eustachian tube.

d) Assessment of resilience of the tympanic membrane by indirect palpation with Tom Cat catheter. An intact tympanic membrane should have more "give" then the more rigid bone of the tympanic cavity. This technique requires experience.

e) Radiology: Ventrodorsal and rostrocaudal open mouth view are useful as both sides of the tympanic cavity can be visualised. Superimposition over other skull parts over the tympanic cavity however complicates interpretation. Minimising superimposition can be achieved with the left (or right) 20^0 ventral right (or left) dorsal oblique view. The neck is extended and a wedge used under the chin to create the desired rotation. In long eared dogs the pinnae must be pulled dorsally to avoid superimposition. The complimentary view must be taken to look at both sides. Alternatively in cats the rostro10^0 ventral-caudodorsal view (closed mouth) gives good images of both tympanic cavities in the one view. General anaesthesia is always needed for obtain good positioning.

f) Positive contrast canalography involves adding 2 to 5 mls of positive contrast and then radiographing to assess for positive contrast reaching the tympanic cavity. This has been shown to be more sensitive than otoscopy, or survey radiography) for detecting tympanic membrane rupture. Interestingly in that same study only 66% of tympanic membranes could be visualised otoscopically in diseased ears and only 74% in normal ears of cadaver dogs (eg about a ¼ of normal ears the TM will not be visible otoscopically).

g) Ultrasound: After filling the ear canal with saline (saline acts as an acoustic window) an intact TM can be visualised a hyperechoic line at the end of the ear canal. Perforation of the TM can be confirmed by finding anechoic saline in the tympanic cavity.

h) Computer tomography: The images have the same physical properties of radiographs but the ability to take cross sectional images overcomes the problems of superimposition. CT distinguishes air and bone well and allows detailed imaging of the middle ear. CT scanning is available at some veterinary referral centres.

i) Magnetic resonance imaging measures radio signals emitted from hydrogen atoms within the body under the influence of a strong external magnetic field. MRI is superior to CT for evaluating the soft tissue densities of the middle ear and for examining the brain. Cortical bone and air have little hydrogen so appear black on MRI. MRI is not as useful as CT for evaluating bony changes in the tympanic cavity.

Advanced imaging (video otoscopy and or CT scanning or MRI) should be offered to all clients where direct visualisation (otoscopy) can not confirm in intact TM, or where indirect measures suggest integrity of the TM has been compromised OR where neurological signs (vestibular or cochlear) exist.

iii. Fixing the Current Problem: Collecting Cytology

In the conscious animal, a cotton tipped applicator is used to collect exudate as deeply as possible in the vertical ear canal/ start of the horizontal canal. Make sure that you not only sample the luminal exudate but that you also slide the bud along the wall of the canal (as firmly as the pet will tolerate). Roll onto a slide and heat fix. Get into the habit of consistently placing samples from left and right ear on the same area of the slide. Diff quick staining is adequate for in-house cytology.

During flushing aspirate contents from the deep horizontal canal using a 5fg feeding tube. The organisms you find in the deep canal are not always the same bugs found in the vertical canal. Compartmentalised infection is uncommon with low viscosity exudates but is common when dealing with ceruminous and keratinous impactions.

Middle ear collection: Where the tympanic membrane is ruptured, a sample can be collected by passing a Tom cat catheter through an otoscopic cone directly into the middle ear. It is usually necessary to cut the end off the tube to allow easier aspiration. If sample is viscous add ½ ml of sterile saline into the tympanic cavity and then aspirate. Where the tympanic cavity is intact but middle ear diseases suspected due to direct observation of fluid through the TM, TM distension, or by advanced imaging then middle ear samples can be collected via myringotomy. Myringotomy requires good visualisation eg, video otoscopy. Myringotomy is usually performed in a dry ear canal after cleaning. A small hole is made using a metal curette or a Tom Cat catheter cut at 60^0 to produce a sharp point. The catheter can then be inserted through the hole to aspirate the sample. Sterile saline can be inserted to facilitate aspiration and gentle irrigation of the middle ear. Injectable enrofloxacin 12.5 to 25mg can be inserted directly into the tympanic cavity if appropriate based on cytological findings.

iv. Fixing the Current Problem: Cytology V Culture

Bacteria and yeast are commonly isolated from normal ear canals. *Staphylococcus spp* (10-20%), *Streptococcus spp* (16%), *Malassezia spp* (15-49%) and *Pseudomonas spp* (0.4%) can be cultured from normal canine ears. In otitis externa the same organisms are often found *Staphylococcus spp* (22-40%), *Streptococcus spp* (10%), *Malassezia spp* (80%) and *Pseudomonas spp* (20%), *Proteus mirabilis* (11%). Routine blood agar aerobic cultures may fail to identify anaerobic organisms and lipid dependent *Malassezia* spp. Cultures are not quantitative. They do not tell you how many organisms are within the ear canal.

Cytology has several advantages over culture

a) Rapid
b) Repeatable
c) Quantitative
d) Low cost
e) Excellent for making empirical therapeutic choices due to established antimicrobial sensitivities.
f) Gives additional information on type of exudate and status of the ear canal that affect therapeutic choices.
g) Excellent for monitoring response (quantitative)

Limitations of culture:

a) Bacterial soup: Duplicate cultures from 15 ears grew the same bacterial species in 13/15 ears HOWEVER only 1/13 showed identical bacterial sensitivities. This suggests that in heavily colonised ears that there may be more than one strain of the same bacteria within the ear OR that there is heteroresistance within the bacterial strain (Griffin 2001).
b) Lack of repeatability. Paired samples from 50 ears, sampled at the same time and location within the ear canal and submitted to the same laboratory had disparate results bin 20% of the samples (10/50). In a further 20% of the samples the bacterial sensitivity results were conflicting (Graham-Mize & Rosser 2004). When triplicate samples of 40 ears were collected and sent to 3 different labs, concurrence on bacterial cultures was achieved on only 17.5% of samples. All 3 labs agreed on Pseudomonas isolation in 17 samples. When MIC (minimal inhibitory concentration) testing was done against 8 antibiotics that labs agreed on only 3/17 samples (17.6%) (Schick et al 2006,2007). Variability in laboratory technique, multiple strains of the same bacteria within the ear or heteroresistance within the bacterial population are all possible explanations.
c) Relevance of the culture result. Culture is a sensitive technique and heavy growth does not equate to large numbers were present in the ear. Cultures are NOT quantitative. Cultures may also miss organism eg anaerobes and lipid dependent yeast.
d) Relevance of sensitivity results. Bacterial sensitivity based on growth inhibition around antibiotic discs *in vitro*, using predicted SERUM antimcrobial levels may be irrelevant to

SURFACE infections treated TOPICALLY because with topical therapy a vastly higher concentration of antibiotic (100-1000x) can be delivered to the site of infection. These high concentrations are pharmacodynamically important for antibiotics known to have a concentration-dependent mechanism of action such as aminoglycosides (gentamicin) and quinolones (enrofloxacin) making bacterial resistance less probable. The use of surrogate discs and addition of antiseptic agents such as Triz EDTA than can alter microbial MICs to antibiotics further reduces the relevance of the sensitivities reported. .

> *Our (MVSC) current advice on use of culture and sensitivity for therapeutic selection is that interpretation of the results is very difficult due to the limitations outlined above. I do not recommend cultures be performed except where there has been failure to empirically chosen treatment where no other obvious cause for treatment failure (poor penetration, poor compliance etc) exists. In those cases I would anticipate that the results would be more repeatable due to selection for a single resistant strain.*
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> *A recent in-house study showed 7/9 Pseudomonas aeruginosa OE cases with reported RESISTANCE to fluoroquinolones on pre-treatment laboratory testing, resolved within 14 days with topical 1.5% enrofloxacin drops and tris EDTA*

v. Fixing the Current Problem

Cytological interpretation. Hope the discussion above has convinced you that cytology is a critical step in managing OE. (Note- specific antimicrobial therapies will be covered later by David Robson)

a) Large numbers of corneocytes (nucleated or anuclear) with no bacteria and variable neutrophils. This indicates the ears are irritated or macerated rather than infected. Normal aural homeostasis is disrupted and these ears are at grave risk of microbial colonization. This is most commonly seen with over zealous use of ear cleaning solutions, alcoholic or acidic ear treatments.

b) Cocci will be *Staphylococcus* spp or *Streptococcus* spp. With studies suggesting coagulase positive *Staphylococcus spp* dominating and it is sensible to base first line empirical treatment based on known *Staphylococcus spp* sensitivities. Distinguishing between *Staphylococcus* and *Streptococcus spp* on cytology is not always possible. Long coccal chains are suggestive of *Streptococcus spp*. While both can form pairs, *Staphylococcus spp* is more likely to form tetramers. Fucidic acid is a good empirical choice for cocci.

c) Yeast (*Malassezia* spp) are retrieved from up to 80% of otitis ears. Dogs with atopy can produce IgE to *Malassezia* and *Malassezia* may activate compliment by non-IgE medicated mechanisms. This means that the degree of inflammation associated with *Malassezia* depends on the HOST RESPONSE rather than the number of yeast. If the ear is inflamed and *Malassezia* are identified then my advice would be to treat the yeast, make sure they are gone by repeating cytology, and then reassess the degree of inflammation in the ear. A good empirical choice for yeast otitis would be the azole containing medications.

d) Rods are rarely found in healthy ears. *Pseudomonas spp* has been reported to be isolated from 0.4% of normal dog ears and *Proteus* sp, *E. coli*, *Klebsiella* sp and *Corynebacterium* sp were not isolated from healthy ears in this study. *Pseudomonas* was isolated from 20% and *Proteus* 11% of otitis ears. The long held dogma that rod otitis require culturing may not be valid (see above). Empirical treatment choices for rod otitis include fluoroquinolones and 3rd generation penicillins

Pseudomonas aeruginosa is a formidable opponent. It has an enormous genome with 10% of that genome involved with regulatory genes encoding pump systems that help with antimicrobial resistance. It has quorum sensing genes that allow intercellular communication and environmental adaptation and can rapidly transfer genetic resistance to antibiotics via horizontal transmission of gene clusters. It has the ability to form biofilms that resist treatment Biofilms may be triggered to form by exposure of planktonic forms to subtherapeutic antimicrobials. Theoretically, hair in the ear canal would provide an ideal substrate for pseudomonas biofiilm formation. Biofilms can result in chronic persistence of the organism.

e) Anaerobic bacteria when seen are usually part of a mixed infection. Anaerobic bacteria, similar to rods, opportunistically colonise the compromised ear canal from the environment. Low oxygen tension in the deep canal associated with inflammation and exudate accumulation creates the required environment for anaerobic survival. Microclimate alteration by effective cleaning and controlling aerobic microbial overgrowth and inflammation may be all that is needed. Occasionally however they appear on cytology as the dominant organism. Penicillins like ticarcillin are effective.

f) 50% of canine otitis externa cases are mixed infections. Cytology, not culture, helps guide your treatment choice based on the dominant organism.

g) Inflammation. Contrary to what is sometimes written the presence of neutrophilic inflammation is not a rule in/rule out for “infection” in the ear canals. Remember that most ear infections are a surface colonisation rather than true infection. Bacterial peptides, toxins and proteases can induce erythema, increased exfoliation, increased cerumen formation, epidermal hyperplasia and pruritus WITHOUT the presence of neutrophils. Identification of the presence of neutrophils is important though due to some medications, like gentamicin, being inactivated in the presence of pus. Neutrophilic inflammation indicates increased host response to the insult and the neutrophilic exudates itself, by virtue of the neutrophlic enzymes, may contribute to the ongoing inflammation and pain. Objectively assessing the degree of inflammation via visualization and cytology impacts on your therapeutic choices. Controlling the inflammation is fundamental to successful management of OE.

Semi-quantitative cytology studies have suggested the following levels as correlated with clinical disease. These should be used as guidelines only as assess in conjunction with the clinical features of inflammation.

a) Malassezia spp 5 or more /hpf (dog), 12 or more/hpf (cat)

b) Bacterial counts of 25 or more /hpf (dog) and 15 or more /hpf (cat)

Note: *Gentamicin and fluoroquinolones have good activity against Staphylococci but NOT against anaerobic Streptococcus spp. Gentamicin is also inactivated by low pH and cellular debris and therefore should not be used where there is effusive exudate unless ears are thoroughly cleaned and kept free of exudate throughout the treatment course.*

Ticarcillin alone is inactivated by penicillinases and therefore is not suitable for coccal infections unless combined with clavulanic acid.

vi. Fixing the Current Problem: Controlling Inflammation.

By definition all cases of OE are going to have an inflammatory component. In some cases the inflammation will be a leading cause in treatment failure if not resolved. Inflammation leads to narrowing of the canal (oedema), increased exudation and pain. It can impact on drug penetration, drug inactivation, as well as have a profound affect on the patient's (and therefore the owner's) compliance. Whenever the EAC if swollen and narrowed due to otitis OR there are significant neutrophils on cytology, systemic glucocorticoids are indicated. Anti-inflammatory doses of 0.5mg/kg sid for 7 to 10 days while initating topical treatment can be extremely beneficial to pain control and improving compliance.

Pre-cleaning treatment with steroids (for 3 to 7 days) is recommended for swollen ear canals to minimise iatrogenic trauma during cleaning and facilitate effective cleaning. Remember that infections of the external ear canal are generally LUMINAL or SURFACE infections and not invasive. This means that topical treatment, that supplies large concentrations of the antimicrobial agent, will not be retarded by the use of systemic steroids. So give the dog steroids. How often do you hear a dermatologist say that!!

Epidermal hyperplasia of the EAC is common in coccal and yeast otitis externa and will occur within days to weeks. We often think of this as a chronic change however it is surprising how often the canal is hyperplastic in "acute" otitis of 1-2 weeks duration. The effect on self-cleaning we will discuss later but in the acute stage this can contribute to poor drug penetration. Resolution of this is usually best achieved with the use of TOPICAL potent steroids like mometasone (**Mometamax ®).**

When animals are present with chronic OE the hyperplasia may be enough to prevent effective access to the EAC. We have already heard the difference in drug levels achieved with topical treatments versus systemic treatments for ear infections. In most cases it is unrealistic to expect resolution of OE by systemic drugs alone. In chronic, severe, hyperplasia I will sometimes inject (under GA) methyl prednisolone (0.5mg/kg maximum TOTAL dose) injected at 4 sites (12, 3, 6 and 9 O'clock position) at the opening of the EAC. Atrophic changes occur within 7 to 14 days and may often then allow application of the mometasone (Mometamax) into the ear canal DAILY for 6 to 8 weeks then twice weekly until maximal improvement

vii. Fixing the Current Problem: Ototoxicity

The old adage “do no harm” applies to otology. Ototoxicity can occur in outer ear canal, middle ear or inner ear and avoidance of ototoxicity should be one of our aims. Visualisation has been discussed and this is critical to establishing the integrity of the tympanic membrane. We also need to be aware of the impact of our treatments on the external ear canal as this may also retard resolution if we make poor choices.

a) Toxicity of the EAC (external auditory canal). Where ulceration is present strong ceruminolytic agents and low pH cleaners should be avoided.

b) Commercial aural products generally contain vehicles like liquid paraffin, sesame oil, mineral oil, plasticised hydrocarbon gel to facilitate transportation of the active ingredients in to the canal. By their nature they tend to be mildly occlusive and increase epidermal hydration so have the potential to cause irritation via macerating the canal. The use of cleaners concurrently with these products may increase that risk. It is sensible to clean the ear, if needed, prior to treatment rather than attempt to do this concurrently. Gels may be less well absorbed than oils and so may be more occlusive. The dose of medication needed for any given ear depends on the length of the canal but also the diameter of the osseous canal. Too big a dose in a dog with a narrow osseous canal will result in the deep portion of the ear canal literally “underwater” for the duration of the treatment period. You must monitor for maceration eg white or grey exudates on otoscopy, nucleated squames and/or neutrophils on cytology without organisms are signs of maceration and treatment needs to be slowly withdrawn.

c) No commercial cleaners or antimicrobial agent, to my knowledge, has a claim for use in the middle ear. Vestibular signs (nystagmus, strabismus, ataxia, head tilt, circling) are obvious to owners. Cochlear changes are not unless profound. The use the brain-auditory-evoked responses (BAER) is giving more insight into middle ear safety. Of the ear cleaners squalene, povodone iodine, 0.2% chlorhexidine and triz EDTA-chlorhexidine 0.15% caused no BAER changes in dogs. Chlorhexidine at the 0.2% caused temporary ototoxicity in cats and concentrations >0.2% may not be safe in dogs.

d) Antimicrobial ototoxicity. A study applying gentamicin sulphate 3mg/ml drops to dog’s ears before and after myringotomy failed to demonstrate ototoxicity. Ototoxicity has been documented with other topically applied aminoglycosides like tobramycin and amakacin. Polymixin B and timentin have also demonstrated cochlear injury (reduced BAER responses) after middle ear treatment. Drugs with good safety profile for the middle ear include fluoroquinolones, clotrimazole, miconazole, nystatin and dexamethasone in aqueous solutions. I am not advocating the use of these products in their commercial form and solubility of the azoles is poor in an aqueous vehicle.

It must be remembered that the disease itself may threaten hearing especially if involving the middle ear HOWEVER every attempt should be made to visualize the TM before treatment and avoid drugs with high potential for ototoxicity when alternatives are available.

viii. Fixing the Current Problem: Compliance

Compliance remains a major issue in veterinary practice and there is nowhere that this is more evident than with ears. Improving outcomes comes down to improving compliance.

Steps to better compliance:

a) Verbal and WRITTEN instructions on both how and why they need to continue and the importance of follow up. An ear may not be cytologically better when the dog feels better.

b) DEMONSTRATE how to apply medications

c) Use a measured dose eg syringe to apply. Rough guide would be 1/3 ml for up to 10kg, ½ ml for 10-20kg, 1ml > 20kg and 1.5 to 2 mls for the all ear dogs eg basset hounds and and bloodhounds. REDUCE dose by ¼ in Spaniels, Staffies, Pugs, Boston terr, Labradors eg dogs with narrow distal ear canal (the osseous canal)

d) Control inflammation with potent topical AND give oral glucocorticoids PLUS give pain relief eg Tramadol for the ulcerated ears.

e) Sedate when examining if the ear is painful

f) Book revisit appointment before client leaves clinic

g) Courtesy (nurse) call after 2 to 3 days to ensure the owners are managing AND reminder call the day before their re-check appointment

h) Ear wicks for aggressive dogs. These are commercially available and can be impregnated with medication and instilled into the ear canal under sedation. They require replacing each 3 to 4 days depending on the condition of the ear. Placing treatment tubes into the canal under anaesthesia and packing the ears with medication soaked gauze may also be tolerated.

ix. Fixing the current problem. Repeat cytology

If we are doing our job right eg we have removed the exudates from the ears, controlled inflammation and pain, treated with appropriate antimicrobial based on cytology, then the ear should feel better rapidly. It is important that owners understand that treatment needs to continue until cytologically cured AND the ear needs to be re-assessed for persistence or re-accumulation of exudates and for maceration. There is no doubt in my mind that many "recurrent" ear infections are actually relapsing infections because of premature cessation of treatment OR a failure to gradually withdraw treatment (in macerated ears) or a failure to address persistent or reformed exudates in the deep canal. The ear is not fixed until it is infection free and free of exudate.

C. Prevent Recurrence

Secondary changes are sequelae that occur due to acute and chronic inflammation of the EAC that when present, will increase the likelihood relapse of the otitis externa IRRESPECTIVE of whether the trigger factor has been controlled. Sequelae secondary to otitis externa include, epidermal and or glandular hyperplasia, inflammatory polyps, fibrosis, stenosis, calcification of the EAC, ceruminoliths, otitis media, cholesteotomas and complete occlusion of the EAC

i. Prevent recurrence: Normalise the ear canal

a) Epidermal hyperplasia:

In long standing cases epidermal hyperplasia (the cobblestone ear canal) may still be present at the time the ear is cytologically cured. Hyperplasia has the potential to interfere with normal lateral migration (self cleaning) of the ear. Continuation of a topical steroid eg mometasone twice weekly for 4 to 6 weeks will often normalise the epithelium. Topical steroids are atrophogenic and for hyperplastic skin this is just what we want.

b) Glandular hyperplasia.

This appears to be a less common reaction to chronic inflammation and is more common in the Cocker Spaniel breed and there may be an idiopathic form in this breed that precedes the onset of clinical otitis. This is less amenable to treatment and glandular hyperplasia may persist post treatment and is often associated with rapid cerumen accumulation, maceration and occlusion of the canal when extensive. Cerumenolytics and drying agents are needed in such cases as long-term maintenance. These dogs are problematic. **Milo's Ear Cleaner ®** appears to be useful in these cases, weekly to twice weekly. Extensive hyperplasia often fails to be controlled and total ear canal ablation and bulla osteotomy (TECA-BO) is indicated in those cases.

c) Stenosis due to fibrosis, calcification or fibrovascular occlusion**.**

Where a patent EAC cannot be achieved via medical means then surgical intervention TECA-BO is indicated. Fortunately this type of ear can be avoided if we follow the rules above. These are end stage ears created by long term treatment failure.

d) Otitis media**.**

Extension of otitis externa to otitis media and a failure to recognise the otitis media may result in ongoing relapse. Visualisation, direct and indirect, is the key. Intra-bulla enrofloxacin, long courses of appropriate antimicrobials (based on cytology or culture??) and surgical drainage (ventral BO) may be required.

ii. Prevent recurrence: Ensure normal self-cleaning

The tympanic membrane appears to play a critical role in the expulsion of cerumen from the EAC. Any trauma or anomaly of the TM can result in a failure of lateral migration and wax impaction. The impacted wax plug further obstructs the epithelium and this leads to the plug increasing with size overtime. In people the diameter of the auditory canal plays a significant risk factor to impaction. Small diameter canal, as in children, dramatically increases the risk. Impact causes irritation and potentially microbial overgrowth.

In dogs we often see wax plugs form in the months AFTER severe otitis externa. My suspicion is that in some cases it relates to the degree of inflammation of the TM (myringitis) at the time of the inflammation in those cases it can be continual problem eg permanent failure of self-cleaning. In other cases I think it reflects a failure of ours to have a clean ear at the end of treatment, often due to retention of medication or macerated epithelium in the deep canal forming the initial impaction. There is no doubt in my mind that the problem breeds are those with a narrow osseous canal (the bony tunnel just in front of the TM). It certainly fits with the human experience of narrow canal leading to increased risk of impaction.

With this in mind I think it is important to re-assess ALL dogs that have had OE about 6 to 8 weeks AFTER all treatment has finished and ensure there is no plug (cerumenolith) forming in the deep canal. If left these plugs can over months/years displace the TM into the tympanic cavity or worse still push through the TM and form a keratinising plug within the middle ear, destroying normal hearing in the process)

For those cases where permanent malfunction of lateral migration has occurred, long term use of a combination ceruminolytic and keratolytic cleaners are required (cleaners are covered later today by David Robson).

iii. Prevent recurrence: Address the WHY

With a first time ear infection, once fully resolved (cytologically cured, normalised, confirmed self cleaning) then it is important that you do NOTHING other than avoid swimming and avoid wetting the ears during grooming and establish whether otitis recurs. There is no need to investigate for causes of RECURRENT otitis if the otitis has not yet proven to be a recurrent disease. If recurrence does occur then knowing what the recurrence interval is and whether there is a seasonal influence on recurrence are useful clues. I stress this point because I see cases of otitis externa where the history is of "prophylactic" ear cleaners being recommended after the first ear infection. Not only do the cleaners change the microclimate of the ear canal, not always for the good of the patient, how do you assess efficacy if you do not have a symptom to monitor? Unless recurrence is documented and recurrence rate known, prophylactic measures cannot be monitored.

With many ear infections the trigger will be obvious eg polyps, neoplasia, foreign bodies, ear mites and the treatment obvious. The difficult cases are where no obvious anatomical or environmental trigger exists OR concurrent symptoms to suggest hypersensitivity disease. In these dogs where there is recurrent OE greater than twice per year allergy investigation, especially atopic dermatitis. Is warranted.

THE FINAL WORD

Below is summary of the common reasons that dogs are referred to us due to treatment failure for OE. Adherence to the basic principles above and will help avoid many of these. Take note of where bacterial resistance sits on this list. The perception of resistance far exceeds the reality!!

Common Reasons For Treatment Failure

a) Failing to adequately clean the ear. Exudate contributes to the pain and inflammation, inhibits penetration of medication and inactivates some medications. A clean ear is half fixed already. Cleaning the ear with a video otoscope is far superior to standard otoscopic techniques.

b) Failing to control inflammation in the ear canal. Both topical and systemic glucocorticoids are indicated for many ears pre and post cleaning. Reducing the inflammation reduces the pain (and increases patient compliance) as well as prevents rapid re-accumulation of exudate within the canal.

c) Inadequate "dose" of aural medications. A measured dose should be applied ranging from 0.3 to 2 mls per dose depending on the size of the dog and the depth and diameter of their ear canal. The owners should be told EXACTLY how much they are required to use and make sure that they are dispensed adequate volume of medication to allow them to continue treatment until the next visit..

d) Poor owner compliance. Approximately 60% of client's referred with pets for relapsing otitis externa claim they have NEVER been demonstrated how to medicate the ears. This I find hard to believe but it does suggest we need to show then more than once and that if ears are failing that we re-assess HOW they are medicating and make sure that this is not part of the problem. Poor pain control, pet's temperament will affect compliance and of course some client's are just "different". For these cases consideration should be given to ear wicks or daily visits.

e) Wrong choice of medication. This involves using good medications but for infections that they are not indicated for. Failure is guaranteed in this case. This has multiple causes and may be due to a failure to perform cytology, trying to interpret culture and sensitivity results without relating this back to your in-house cytology, failing to sample both vertical and horizontal ear canal, and using medications that are inactivated by low oxygen tension, low pH and nucleic acids in the presence of purulent exudate.

f) A failure to re-assess the patient, confirm cytological resolution. ALL otitis cases should be re-examined weekly to each 14 days until resolution.

g) A failure to address secondary changes eg epidermal hyperplasia, glandular hyperplasia and failure of “self cleaning” and otitis media. This largely relates to inadequate visualisation due to a failure to clean the ear and examine the deep structures of the ear canal or simply the inherent limitations of standard otoscopic examination.

h) Bacterial or fungal resistance. Often blamed but the reality is that this is a surprisingly uncommon cause of failure and when it occurs it has generally been created by long-term failure due to the other factors mentioned above.

i) Maceration due to use of diluted shampoos and overzealous use of ear cleaning agents.

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Chapter 12

Antimicrobial Therapies in Otitis

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INTRODUCTION: THE PHILOSOPHY OF EAR ANTIMICROBIALS

Similarly to ear cleaning, there is a paucity of reliable evidence-based medicine investigating appropriate antimicrobial therapy in otitis externa and media. That does not mean there is a shortage of studies on the topic, but the inherent variability between ears, patients, diagnostics, investigators and cleaning and drug protocols make meaningful comparisons nearly impossible. Indeed, the only evidence-based review on the topic, which specifically examined treatments for *Pseudomonas* otitis came to the conclusion that there was insufficient evidence for or against recommending the use of any of the treatments examined, largely because no two trials used the same protocols and there were no randomised controlled trials at all (Nuttall & Cole, 2007). However, just because there is an absence of clear evidence to base treatment options on, should not mean clinicians cannot treat these conditions. On the contrary, there is likely more than one way to achieve a successful outcome in any given case where medical therapy is feasible.

What follows then is again the author’s opinions and experiences on the topic, coloured by other dermatologists’ published opinions and backed wherever possible by peer-reviewed studies.

TOPICAL VS SYSTEMIC THERAPIES

In the Treatment of Otitis Externa

Topical therapy is key to the successful resolution of the majority of cases of otitis externa, which is essentially a surface infection. Penetrating this ‘‘vat’’ of infection is best accomplished by the application of sufficient volumes of a topical antimicrobial. Essential to this therapy though, is successful removal of exudate. If the medication cannot penetrate the full length of the canal, then treatment is bound to fail. The choice of appropriate active ingredients and vehicles for treatment of otitis externa is usually made empirically, based on cytological examination of ear canal exudates and otoscopic examination of the inflamed canals. Culture and sensitivity to determine selection of topical medications is inappropriate, especially with concentration dependent antimicrobials, because

- topical medications can achieve 100-3000 times the serum concentrations achieved by systemic medications (on which sensitivities are based) and can simply overwhelm bacterial resistance mechanisms
- concurrent use of antiseptic cleaners can further reduce the minimum inhibitory concentrations of micro-organisms present in the canal
- some antibiotics present in a formulation are synergistic
- some otic actives are not present on sensitivity panels.

What has not been studied is the degree of penetration of topical antimicrobials into the intact or inflamed canal wall.

In contrast, systemic (oral) antimicrobials are unlikely to achieve therapeutic concentrations within the fluid and waxy exudates of the external canals in which the infectious organisms are harboured, because adequate concentrations of antimicrobial (which reach the MIC for the organism) may not even be achieved at the surface of the external ear canal epithelium. Exceptions to the rule may be where the ear canal epithelium has been eroded or ulcerated extensively, or azole antifungals, which are known to bind to keratin and sebum and are present in the stratum corneum (further details below). Systemic medications may be of some use in a bacterial otitis externa where there is a folliculitis or furunculosis in the canal wall. In the author’s experience (as well as in the literature), only rarely can systemic medications completely resolve an otitis externa.

In the Treatment of Otitis Media

In contrast, the middle ear (tympanic bulla) contains a highly vascular mucous membrane lining, which may allow for better diffusion of drugs from the vascular compartment to the bulla space. The choice of systemic antibiotics for treating the middle ear compartment is preferably based on culture and susceptibility testing, though for some more resistant infections, there may be few practical options for systemic therapy.

Thorough lavage of the bulla to remove infective and inflammatory exudates is essential for any medical management of otitis media.

In the case of bulla impaction with inflammatory exudates and debris, medical failure is virtually guaranteed without an effective lavage. This is especially important for topical therapy of otitis media.

Topical therapy of otitis media is somewhat controversial. In fact, it has been stated that otitis media cannot be resolved with topical therapy alone. The author (amongst others) would disagree with this for a substantial portion of cases. However, because of ototoxicity issues (vestibular disease and deafness) associated with many topical otic products, there are only a limited number of medicines that can be infused into the bulla. While no drugs are licensed for the treatment of otitis media in the dog or cat, drugs recognised as having a high degree of middle ear safety include the fluoroquinolones (ciprofloxacin, enrofloxacin, ofloxacin, marbofloxacin), aqueous semi-synthetic penicillins (penicillin G, carbenicillin, piperacillin-tazobactam but NOT ticarcillin), some cephalosporins (ceftazidime, cefmenoxime), azole antifungals (specifically clotrimazole and miconazole but it has been reported all are safe), nystatin (though persistence of residue may be a concern), tolnaftate, aqueous glucocorticoids (dexamethasone, flucinolone), squalene, tris EDTA and chlorhexidine (<0.2% and in dogs only). While gentamicin has been reported as being ototoxic, an aqueous formulation 3mg/mL has been used topically bid up to 21 days in dogs with ruptured TMs with no adverse reactions. The clinician should also be aware that while some of these drugs may be safe to use in the middle ear, the vehicles they are delivered in may not be (see below).

Several techniques for topical therapy of otitis media have been described:

- Following bulla flushing and subsequent aspiration of flush fluid, direct infusion of topical medications into the bulla is performed via feeding tube through the otoscope. The bulla is a blind pouch with poor drainage, so medication can remain in the bulla for 4-5 days with each application. Bulla infusions provide extremely high levels of antibiotics, antifungals, or corticosteroids. The initial bulla infusion is limited to the open space in the bulla, which increases as inflammation subsides. After a week, a short GA is repeated and more medication is infused. (Gotthelf 2005)
- Following bulla lavage, high through-put topical therapy is performed. This entails application of large volumes (1–2 mL) of topical drug twice daily and regular (daily or every other day) at-home flushing of the canals using an antimicrobial cleanser. It is suggested that high-volume application of low-viscosity antimicrobial preparations and cleansers promotes a

continued ‘‘flushing’’ of the bullae as long as the tympanic membranes (TMs) remain open. (Morris 2004)

TOPICAL DELIVERY OF MEDICATIONS

Compliance & Administration

While topical treatment of otitis externa is optimal, there are several challenges to successful administration. These include otic pain, otic stenosis, patient temperament & client capabilities and correct medication instructions. While these can be significant short term challenges, it is important to focus on the end goal. A failure to manage otitis correctly and aggressively enough can lead to months to years of patient discomfort and client frustration.

Pain

Pain in the pet, or the perception of it by the owner can make administration of medication difficult. This needs to be aggressively managed. See the previous lecture for options.

Otic Stenosis

A patent ear canal is mandatory for effective topical drug administration. Temporary stenosis from inflammation should be managed with glucocorticoids orally, topically and intramurally if required (see previous lectures for details). Some cases of inflammatory otitis may be managed with prolonged use of potent topical anti-inflammatories alone, with the canal progressively opening as the medication is able to penetrate deeper into the canal. If a canal is permanently narrowed through anatomy, scarring or glandular changes, then use of more fluid rather than viscous otic formulations may be required for deep penetration of the ear. Permanent stenosis at the entrance to the canal may be able to be managed surgically (Zepp’s, lateral canal ablation) to better facilitate long term medication administration if required.

Patient Temperament & Client Capabilities

Even in medically ideal cases, topical therapy may be challenging because of the temperament of the patient, or the client’s ability to administer medications. While the former (and part of the latter) problems may be addressed in the medium to long term with behaviour modification, it is a short term challenge. A compromise solution may be the use of ear wicks, boarding the animal at the clinic, or once daily administration of medications by the veterinary staff either at the clinic or the owner's residence. A week of correctly administered medication is far more likely to be beneficial than a much longer period of incorrectly administered medication.

Correct Medication Instructions

Clients may need to be shown how to administer medications correctly. Failure to do this is a significant cause for treatment failure. Equally, for otitis externa, clinicians need to ensure that an adequate volume of medication is delivered to line the entire canal. The author gets clients to use Terumo 1mL syringes (the brand least likely to 'bung up' quickly with some ear ointments in the authors opinion) to both accurately measure ear medications and dispense them into the ear canal. A broad guideline (depending on the diameter and length of the ear canal) would be 0.15-0.2mL for a cat, 0.6mL for a Labrador and 1.0mL for a German shepherd or very large dog. Twice daily dosing may require slightly small volumes to avoid overdosing. Getting clients to count drops increases the time of administration and fundamentally means the nozzle of the bottle is not in the canal, reducing penetration of the medication. Putting the nozzle in the canal and telling clients to use 'a squeeze' means that both under and over-dosing are risked because the amount of medication is not measured out.

Success or failure of topical drug administration can be assessed at follow up. Improvement in cytology and gross canal appearance are strongly supportive of successful administration, but if these are not improved as well as expected then it can be difficult to differentiate a compliance failure from a medication failure. In this case, two clues that may suggest a compliance failure are absence of being able to visualise topical medication in the canal and not just on the pinna (easier with ointments because they stick around), and also microscopic visualisation of drug crystals on otic cytology.

Vehicles: Advantages and Limitations

Most commercially produced topical products contain one or more active ingredients (antibacterial, antifungal, and anti-inflammatory) in various combinations as well as a vehicle and various solubilisers, stabilisers, and surfactants. These are not necessarily all listed on the product as there is no regulatory requirement to list complete formulations of veterinary pharmaceuticals in Australia. The formulation of the topical product with regard to the vehicle may be as important as the active ingredient to the success of therapy.

Vehicles are chosen by drug manufacturers to maximize drug solubility, to maintain drug activity locally for the maximum period, and to minimize systemic absorption. They may also have some degree of antimicrobial activity. Vehicles inherently will interact with the skin of the ear canal in some manner, and also have potential side effects. All these things should be part of the consideration in medication selection but in general:

- dry, scaly, crusty ear canals are benefited by oil or ointment bases (e.g. Mometamax, Intervet Schering Plough), which help to moisturise the skin, and may be aggravated by alcoholic (e.g. Delmycin, Ceva-Delvet) or macerated by highly aqueous vehicles
- ceruminous ears may respond better with a straight paraffin, which is a cerumen softener (e.g. Surolan, Ausrichter), or alcoholic vehicle
- occlusive ointments or oils may be inappropriate in purulent exudative ears without aggressive cleaning and inflammation control
- creams or vehicles that are too ‘stiff’ are frequently poor choices, especially in stenotic canals because the client may have difficulty getting the medication to the horizontal canal.

More choices are available when ear medications are compounded.

Saline

At body temperature saline is a middle ear safe vehicle for a variety of water soluble antibiotics. Unfortunately, it can lead to maceration of the ear canal with prolonged use and increase the risk for yeast overgrowth.

Propylene Glycol

Propylene glycol is a slightly more viscous vehicle than saline and an excellent solvent for many drugs. It is an effective ceruminolytic when neat, and may be so at concentrations above 40%, and has significant antibacterial and antifungal effects. It also is hygroscopic and humectant, more so at higher concentrations. At high concentrations (60-75%) also it is keratolytic and denatures protein which can be very useful in hyperkeratotic ears and purulent ears but can be counterproductive long term in more normal ears. It is however ototoxic and should not be used where there is either a perforated TM, or a suspicion of one. It can also occasionally trigger a topical drug reaction.

Hypromellose

Hypromellose, or hydroxypropyl methylcellulose is a colloid solution used as an ocular lubricant (Methopt Tears, Sigma Pharmaceuticals – available in a 15mL bottle). As a colloid it absorbs water, and avoids maceration of the ear canal. Studies in guinea pigs and anecdotal reports in dogs support its safety in the middle ear.

Squalene

Squalene is a natural hydrocarbon which is a precursor for cholesterol. It is found naturally in human sebum and canine cerumen, and makes up approximately 12.5% of the latter. It is somewhat viscous (and can be a little messy) but can act more successfully as vehicle for relatively insoluble drugs (such as ketoconazole) that need suspension. Squalene is absorbed somewhat by the ear canal and can act as a cerumen softener. Importantly, it is middle ear safe.

Ear Wicks

Ear “wicks” are polyvinyl acetate, highly absorbent sponges that can be placed in the ear under anaesthesia. On removal from the packet they are dry, small and tightly compressed, and they expand once hydrated. The wick soaks up discharge when rehydrated with ear medications facilitate treatment of the skin surface around the wick. Gauze ribbon has been used as an ear wick in humans with success (and also in one case of the author’s) but tends to come out of the ear more easily.

Wicks are indicated in patients

- who are difficult to medicate
- have stenotic proliferative otitis (wherein it is difficult to get medication where it needs to get to in the ear)
- where there is a ruptured TM and potentially ototoxic medications are indicated for the external ear canal

The author has found the most easily available in Australia are Pope Oto-wicks. They may be either fenestrated (with a hole in the middle) or non-fenestrated (aka Merocel Oto-wicks). They are available in 15mm or 24mm sizes. For most dogs a 24mm size and non-fenestrated wicks are appropriate. Use of fenestrated wicks has been reported for *Pseudomonas* otitis, and also after surgical procedure in the lumen of the ear.

They are typically placed under GA following an ear flushing procedure, and replaced every 3-5 days if required under heavy sedation or repeat GA. It is not uncommon for wicks to fall out prematurely. In dogs they have been reported to be well tolerated - their use is not well reported in cats.

Ear wicks are designed for use with aqueous solutions and expand rapidly following exposure to them. In contrast, oil-based ear drop preparations fail to expand the wick. This needs to be considered when planning their use. Selection of appropriate ear medications for use in the wick depend (as always) on cytology, state of the TM, level of inflammation, and maybe, *in vitro* sensitivity results.

Aqueous antimicrobial solutions planned: The dry wick is placed in the ear canal and held in the desired location using biopsy forceps or alligator forceps. Depending on the case this may be done through a hand held otoscope. The wick is then rehydrated with slow direct application of the antimicrobial solution, using a feeding tube if required. This minimises the risk of non-middle ear safe solutions going past the wick. The wick may be placed with the head dorsal rather than lateral to further minimise this risk. Once the wick is rehydrated it should fit snugly to the canal wall. Further medication may be added to the wick at this point.

In cases of *Pseudomonas* otitis, a combination of fluorinated quinolones and tris EDTA or Ticarcillin, and tris EDTA has been reported for use in the wick. The compounded solutions listed in Appendix C are appropriate for this use also and contain glucocorticoids.

If possible, small amount of ear solution can be placed each day in the ear by the client at home to ‘top up’ the wick.

Non-aqueous antimicrobials planned: The wick is hydrated using just enough sterile saline, water for injection or tris EDTA for the wick to expand. Ear ointment drops are then applied to the outside of the wick and allowed to be soaked up. Ointments do not transfer well within the wick and will need to be applied to all sides. Approximately 1.5mL of ointment will completely fill a wick. The author has used Canaural (Bayer) in this manner successfully. The use of certain ointments can also lead to premature breakdown of the wick. Further reports are required on this technique.

Adrenal Function and Topical Glucocorticoids

Several studies have examined the effects of otic medications on the pituitary adrenal axis, predominantly in small breed (<14kg) dogs. Most of these have used manufacturer recommended doses, which tend to be on the low side in the authors opinion (e.g. for Otomax, 4 drops per ear twice daily). Despite this, after 2 weeks, significant suppression of cortisol on an ACTH stimulation test was noted for a 0.1% dexamethasone commercial product (66-100% of cases depending on the study), Panalog (Novartis) (17-100% of cases) and 0.1% dexamethasone in saline (57%). Otomax, Mometamax (Intervet Shering Plough) and 0.01% dexamethasone did not record any significant ACTH suppression at recommended doses. Whether this still applies at higher doses, or whether adrenal suppression is still seen in larger dogs is unknown. However, clinicians should be aware of the possible risks of iatrogenic hypercortisolism from topical medications.

Prolonged use of potent steroids in the ear canal risks possible delay of wound healing, skin atrophy and anecdotally may increases the risk of calcification. The author tends to use aggressive topical glucocorticoid doses in severely inflamed ears in the initial phase of therapy.

Duration of Therapy

Key to successful management of otitis externa is continuation of therapy until the infections is clear, and until the ear canal is as normal as possible. Premature cessation of therapy is a common cause for relapsing problems.

Otitis Externa

For acute disease, a minimum of 5 to 14 days therapy depending on the degree of inflammatory changes (oedema, hyperplasia, and erosion/ulceration) is to be expected. However, rechecks are mandatory every 1-2 weeks to ensure that ears are cytologically and otoscopically resolved prior to cessation of therapy. It is not uncommon to have a dog clinically resolved with otoscopically normal ears because of anti-inflammatory medications, where cytology is still not normal. Clients cannot be relied upon to make this judgement.

For chronic otitis with more significant canal wall changes, the client should be prepared for longer term topical therapy (at least 4 weeks in duration) even following flushing. In extremely chronic cases, several months of rigorous topical therapy may be necessary to return the external canals to their normal state. Rechecks should be scheduled every 2 to 4 weeks for cytological and otoscopic examination until complete resolution is achieved.

For ears with extreme inflammatory changes, and where there is any questions over whether therapy will work OR in chronic cases where medications are being tapered and there is a higher risk of relapse, then rechecking every 7 days is appropriate. The author has experienced cases where severe relapse can occur even within this time frame with inappropriate medication.

Otitis Media

It has been reported that the successful therapy of bacterial or fungal otitis media relies on an initial thorough cleansing of the bulla, and aggressive targeted antimicrobial therapy for an absolute minimum of 6 to 8 weeks. Similar to otitis externa, rechecks are mandatory every 2 weeks until the ear canals are negative for microorganisms on cytological examination, the external canals have no residual oedema, and the epithelium has normalised.

Once this is achieved, reassessment of the middle ear is more challenging. Initially the TM should be re-examined for signs of bulging that may indicate fluid accumulation, and that the TM has healed. If any neurological signs were present initially then a neurological examination should be repeated to assess for changes. If the bulla was radiographically abnormal (or abnormal on CAT scan or MRI if available) at the time of diagnosis then repeat imaging is a useful tool for reassessment. If there is reaccumulation of material then consideration needs to be given to repeat myringotomy, or changing to surgical management of the bulla.

If the bulla is normal by all levels of assessment, then the options are to continue systemic therapy until it has been continued for a total of 6-8 weeks, or to stop therapy. One report showed a mean time to resolution in chronic otitis media was ~86 days (range 30-360 days). It may well be that an acute otitis media does not need therapy for such a long period.

PRINCIPLES OF THERAPY OF OTITIS: SUMMARY

When considering the therapy of any case of otitis, there are five basic principles that should to be considered, even if all of them don't always apply to every case:

1. Clean the ear. Failure to clean the ear will often result in failed therapy.
2. Once the ear is clean, use disinfectants to assist antimicrobials, minimise the chance of resistance and keep the ear clean
3. Use topical antimicrobial therapies. They provide more activity where it is needed to clear infections.
4. Control inflammation. Inflammation makes administration of medication harder, creates and environment favourable to persistence of disease and causes patient discomfort.
5. Use systemic therapy where required. Considerations for its use include canal furunculosis, otitis media, and adjunctive therapy where topical therapy application is less than ideal.

The following sections are based around this scheme.

ANTIMICROBIAL THERAPY FOR EARS WITH MAINLY YEAST ON CYTOLOGY

Aetiology

In Australia, the majority of yeast seen on otic cytology are *Malassezia pachydermatis*. Less common yeast species isolated include *M. globosa*, *M. furfur*, *M. sympodialis* and *Candida* spp.

Diagnosis

In studies examining the correlation of cytology with otitis, high yeast counts generally correlated well with clinical signs.

> Cytology in normal dogs: <1 yeast per 3 1000x oil immersion fields (OIFs)
>
> Cytology in dogs with otitis: >0.8-1.6 yeast per 1000x OIF
>
> Cytology in normal cats: <1 yeast per 3 1000x oil immersion fields (OIFs)
>
> Cytology in cats with otitis: >1.92 yeast per 1000x OIF

However, it can be clearly seen that there is a grey zone in cytology between normal and abnormal ears, and in all cases cytology should be considered in combination with clinical signs (or lack thereof) and examination of the ear before a diagnosis is made. Normal dogs and cats may occasionally carry higher than normal numbers of yeast asymptomatically (esp. if atopic). In contrast, some cases may have profuse inflammation or pruritus in the face of relatively low numbers of organisms. In the authors opinion, this may be a clue to possible IgE-mediated *Malassezia* hypersensitivity in that patient.

Topical Antifungals

Disinfectants

These are useful as a sole therapy where there are low numbers of yeast and minimal inflammation, or occasionally in cases apparently resistant to other antifungal ear medications. The only two with proven efficacy against yeast are EpiOtic (Virbac) bid x 14 days (68% resolution in a variety of infections but 80% still had mild-moderate ear exudate), and Malacetic Otic (Dermapet) q24h x 7d then twice weekly (86% cytological resolution but irritation occurred in approximately 1 in 6 dogs). Neither are particularly effective ceruminolytics so penetration is an issue where there is significant exudate. Milos' Ear Cleanser (Ceva-Delvet) is likely to have activity against yeast based on overseas studies looking at similar products but remains untested for this purpose. It is a more effective ceruminolytic. None of these are middle ear safe.

Antifungal Ear Products

Any of the major commercial combination ear products (with the exception of Baytril Otic) is likely to be reliable in the therapy of an uncomplicated yeast otitis. However, cases of product failure in cases of *Malassezia* otomycosis where other causes of failure have been ruled out have been reported by the author and others to all the major commercial products. Otomax has tended to be over-represented in the author's experience but this may be a reflection of usage patterns at his practice. A subsequent investigation of these cases revealed significant resistance to clotrimazole and / or miconazole but not nystatin in several investigated cases. While this confirmed the presence of azole resistance in the authors practice, it also suggested that some cases were pharmacological failures rather than true resistance.

First line topical antifungals include:

- Surolan (Ausrichter): Tend to use this when there is a little more exudate and no other cleaner is being used as the paraffin vehicle is a good cerumen softener

- Otomax (Intervet Schering Plough): Preferred to Mometamax (Intervet Shering Plough) because of twice daily clotrimazole dosing where possible.
- Mometamax (Intervet Schering Plough): Used where dosing is an issue or more marked inflammation is present.

Second line topical antifungals include:

- Canaural (Bayer): In case of azole failure. The author prefers this vehicle to Panalog (Novartis) which also contains nystatin.

Others registered antifungal medications in Australian ear products include undecyclenate, monosulfiram, nitrofurazone and dichlorphen. These ‘legacy’ antifungals have been poorly studied in the last 40 years and while they may be effective, it is difficult to assess this objectively.

None of these medications are middle ear safe and are inappropriate to use where the TM is ruptured. Where topical antifungal activity is required and the TM is ruptured, options include

- use of ear wicks as previously described using one of the products above
- aggressive systemic antifungals (though this can be unreliable as a sole therapy – see below)
- use of a middle ear safe compounded antifungal (such as 2% ketoconazole in squalene suspension)
- use of 2% acetic acid / 2% boric acid aqueous solution (middle ear safety anecdotally OK but not well investigated)

Systemic Antifungals

Systemic use of antifungals are a consideration where there is:

- fungal otitis media
- sole or adjunctive therapy where topical medications are not possible or there are severe proliferative changes in the ear canals
- as a preventative for fungal overgrowth when a bacterial otitis is being treated without use of topical antifungals

While the use of systemic antifungals for the treatment of yeast otitis externa is reported by several authors, there is only a single study that has examined this use. In this study 13 ears amongst 20 dogs with *Malassezia* otomycosis and/or dermatitis were treated with itraconazole orally (n=10/group), using either a pulse administration regimen (5 mg/kg PO q 24 h for 2 consecutive days per week for 3 weeks) or once daily administration (5 mg/kg PO q 24 h for 21 days) with no other medications. However, when cytology scores only for ear samples were analysed, the day 21 score was not significantly decreased compared with day 0 score for either group. The range of responses in ear cytology was very wide, with a few responding nearly totally, most improving somewhat and a few worsening (up to 71% greater than the original count). This strongly suggests that itraconazole, at the doses and durations examined, is unreliable as a sole treatment of *Malassezia* otomycosis. Higher doses or longer durations may be more efficacious, but in dogs there is an approximately 7% risk of inducing a cutaneous vasculitis drug reaction at 10mg/kg/day dosing and likely also a greater risk of inappetance, vomiting and drug induce hepatopathy. This dose is not recommended for routine use. Most cases will still require topical therapy to completely resolve, despite the fact that itraconazole binds to keratinocytes and persists in the skin (which is why the pulsed therapy was effective elsewhere on the skin).

This contrasts with the anecdotal response to ketoconazole reported by many dermatologists. There is some pharmacokinetic logic to this as ketoconazole is found in very high levels in humans in the sweat and stratum corneum, and given that cerumen is a product of modified apocrine glands, it suggests that ketoconazole may concentrate better in cerumen than itraconazole, which is found more in stratum corneum and sebaceous exudates. Fluconazole also is found at a higher concentration in human sweat (at a much higher concentration compared with plasma) and may be a better choice for yeast otitis, however, *in vitro* sensitivities to this azole are not as good as other, so its usefulness remains to be investigated.

Concentrations of systemic antifungals in the middle ear have not been reported but given that most of the major antifungals concentrate in the stratum corneum by back diffusion via sweat or sebum to a concentration much higher than plasma levels, achieving high antifungal concentrations in the bulla may take more aggressive doses, and more prolonged dosing.

First line systemic antifungals:

- Otitis media (dogs): ketoconazole (Nizoral, Janssen) 10-20 mg/kg/day, itraconazole (Sporanox, Janssen) 5mg/kg q24h x 4-6 weeks

- Otitis externa (dogs): ketoconazole (Nizoral, Janssen) 10-20 mg/kg/day
- Otitis media or externa (cats): itraconazole 10mg/kg q24h x 4-6 weeks

Second line systemic antifungals:

- Otitis media (dogs): terbinafine 30 mg/kg q24h x 4-6 weeks
- Otitis externa (dogs): fluconazole 2.5-10 mg/kg q24h
- Otitis media or externa (cats): fluconazole 2.5-10 mg/kg q24h, terbinafine 30 mg/kg q24h x 4-6 weeks

ANTIBIOTIC THERAPY FOR EARS WITH MAINLY RODS ON CYTOLOGY

Aetiology

In Australia, the majority of rods identified on culture are *Pseudomonas aeruginosa*, with *Proteus* spp. and *E. coli* both identified at about 11-20% of the frequency of *P. aeruginosa*. Other less common rods include *Corynebacterium* spp. (often listed as diphtheroids on reports) and *Klebsiella* spp.

While *Corynebacterium* is not uncommonly found on culture from ear with otitis, it is usually present as part of a mixed culture and it currently thought to be a 'passenger' organism rather than a true pathogen. If present in pure culture though it should be treated for specifically.

Diagnosis

In studies examining the correlation of cytology with otitis, high bacterial counts generally correlated well with clinical signs.

Cytology in dogs with otitis: >4 bacteria (rods or cocci) per 1000x OIF

Cytology in cats with otitis: >2.4 bacteria (rods or cocci) per 1000x OIF

Rods are not reported at all on cytology from normal dogs, though at the authors practice the occasional atopic dog is seen with a few rods in the ear in the absence of signs of otitis. Again, this leaves a grey zone in cytology between normal and abnormal ears, and in all cases cytology should be considered in combination with clinical signs (or lack thereof) and examination of the ear before a diagnosis is made.

On cytology, *Corynebacterium* can be distinguished morphologically in some cases as they are slightly large rods with less even staining characteristics compares with the other common aerobic Gram negative rods.

While many authors recommend routine culture of all cases of rod otitis, given the limitations of culture (previously covered by Greg Burton) when it comes to ear infections, this is not the rule at the author's practice. The recommendations for culture there are to consider culture where

- there has been failure to empirically chosen treatment where no other obvious cause for treatment failure (poor penetration, poor compliance etc) exists
- otitis media
- unusual infective organisms are observed as a dominant organism on cytology
- systemic therapy is deemed necessary

Topical Anti-Rod Antibacterial Therapy

Disinfectants

Use of disinfectants is mandatory is all cases of pure or predominantly rod otitides. In the absence of culture to confirm a diagnosis to the contrary, it should be assumed that *Pseudomonas aeruginosa* is likely the dominant bacteria in these cases. Several disinfectants have been shown to be bactericidal for *P. aeruginosa*, or at the very least lower the MIC including not just silver sulfadiazine, tris EDTA and acetic acid, but also EpiOtic (Virbac), and an ear cleaner of similar formulation to Milo's Ear Cleanser (Dermapet). They are also important for controlling recurrence of exudate. Their use and efficacy is another reason *in vitro* sensitivities are largely irrelevant for topical therapies. One limitation, however, is the ulceration present in most of these affected ear making them susceptible to pain and irritation by several of these products.

For this reason the best time to use acetic acid is while the patient is under GA. The author's choice if the TM is intact is Malacetic Otic (Dermapet) or 2% acetic acid / 2% boric acid aqueous solution if it is not. It is left to soak for several minutes before being aspirated out again to minimise subsequent discomfort. Any flush that lowers the pH of the ear should not be used directly with either fluorinated quinolones or aminoglycosides. A period of about 20 min should be left between flush and antibiotic administration. Alternatively the flush solution should be neutralised with tris EDTA before antibiotics are applied.

The broad rule for home therapy is 'all cases of rod otitis go home with tris EDTA'. Tris EDTA (ethylenediaminetetraacetic acid tromethamine; Triz EDTA, Dermapet) has several beneficial mechanisms including:

- damaging bacterial cell walls (esp. Gram negative) allowing greater antibiotic penetration and leading to possible bacterial death without further treatment
- probable inhibition of cell wall efflux pumps (thereby interfering with some bacterial resistance mechanisms)
- alkalinisation (many antibiotics work better in an alkaline pH)
- chelating of free metal ions, which prevents degradation of penicillins and increases aminoglycoside activity

Further more, tris EDTA is middle ear safe and is non-irritating. The authors use Triz Plus (Dermapet, now called TrizChlor) which also contains 0.15% chlorhexidine as this has been shown to have better activity and is still middle ear safe. Unfortunately this is not currently commercially available in Australia. Tris EDTA is typically used as an ear soak approximately 10 minutes prior to antibiotic administration, though some authors have recommended making up enrofloxacin (to a 10mg/mL final concentration) with the Triz EDTA (see Appendix C). Tris EDTA has less activity against non-*Pseudomonas* Gram negative rods.

In cases of resistant *Pseudomonas*, use of more than one antiseptic may be a consideration. In these cases, use of silver sulfadiazine (Baytril Otic, Bayer) or, if the inflammation is well controlled, 2% acetic acid / 2% boric acid are both considerations though the latter if used should be dosed about 20 minutes prior to tris EDTA and antibiotics. Middle ear safety of Baytril Otic (Bayer) has not been published.

First line topical anti-rod disinfectants:

- Under GA at flushing only: Malacetic Otic (Dermapet) if TMs are intact, aqueous 2% acetic acid / 2% boric acid if not
- Home therapy prior to antibiotics: Triz EDTA (Dermapet); TrizChlor (Dermapet) if available

Second line topical anti-rod disinfectants:

- Home therapy: Baytril Otic (Bayer) for silver sulfadiazine once daily following Triz EDTA; Malacetic Otic (Dermapet) if TM is intact, aqueous 2% acetic acid / 2% boric acid if not once daily 20 minutes prior to Triz EDTA but only if inflammation is controlled

Topical Antibiotics

The key requirements for empirical selection of antibiotics for treatment of rod otitides are efficacy against commonly isolated organisms. In Australia, this means efficacy against *Pseudomonas aeruginosa*, *Proteus* spp. and *E. coli*. The best first line selections for this are enrofloxacin and gentamicin. Both are concentration dependent antibiotics, both perform better at alkaline pH and both are synergistic with tris EDTA.

The major differences are that the performance of gentamicin is degraded by organic debris and purulent exudate, so the ear needs to be kept spotlessly clean, and inflammation well controlled for best effect, and that gentamicin (in the commercial forms) are not middle ear safe, unlike enrofloxacin. For this reason in most cases, and also because of its high topical concentrations and concurrent use with tris EDTA, even where *in vitro* resistance (which is common in Australia – 442/1256 cultures were resistant *in vitro* in a recent report) is reported (Bagg 2009), enrofloxacin is the author's first line topical therapy for rods. This approach is reinforced by (as Greg Burton previously reported), the recent in-house study that showed 7/9 *Pseudomonas aeruginosa* otitis externa cases with reported resistance to fluoroquinolones on pre-treatment laboratory testing, resolving cytologically within 14 days with topical 1.5% enrofloxacin drops (with and without Triz EDTA). The author more frequently uses a compounded enrofloxacin ear medication (see Appendix C) to achieve a higher concentration of enrofloxacin than is commercially available, and to add in a topical glucocorticoid. The vehicle used depends on the state of the TM (see Appendix C).

In cases where enrofloxacin or gentamicin are inadequate or inappropriate, the author's next step is Timentin (GlaxoSmithKline) 6% (see Appendix C) but this has been reported to cause hearing deficits in cases where the TM is perforated. In the rare instance where further antibiotic selection is required the next major considerations include tobramycin and amikacin, though these are not middle ear safe (see Appendix B).

One risk with use of aqueous antibacterials only (esp. Timentin) in the treatment of otitis is that of yeast overgrowth. This can be a significant complication, especially when the TM is ruptured, as management of yeast otitis media can be challenging. Anecdotally, use of propylene glycol (where the TM is intact) or Methopt Tears (Alcon Laboratories) (where the TM is perforated) as a vehicle reduces this problem.

Some veterinarians have recommended use of imipenem or piperacillin and other 3rd generation cephalosporins to be diluted and used as ear drops for resistant *Pseudomonas*. This practice should be seriously questioned as these are some the most effective rescue drugs for serious human infections and indiscriminate use in the veterinary field could jeopardise their value. There has only been one case at the author's referral practice, where several hundred cases of otitis are seen annually, in 10 years where this possibility was considered.

First line topical anti-rod antibiotics:

- TM intact or ruptured: enrofloxacin 1.5% with dexamethasone NaP depending on inflammation and vehicle depending on the state of the TM (see Appendix C)
- TM intact and inflammation controlled: Otomax (Intervet Schering Plough) q12h, Mometamax (Intervet Schering Plough) q24h

Second line topical anti-rod antibiotics:

- TM intact: Timentin 6% q12h

Third line topical anti-rod antibiotics:

- TM intact: 30-50 mg/mL amikacin q12h, 3-8 mg/mL tobramycin

Systemic Anti-Rod Antibiotics

The benefit of systemic antibiotic therapy in the management of otitis externa is controversial. There is again only a single study that involved treating *Pseudomonas* otitis with a systemic antibiotic alone. Of 54 cases of otitis externa treated with oral marbofloxacin 5 mg/kg q24h for either 21 or 42 days depending on response and following saline flushing, 27.8% of cases resolved, 42.6% improved and 29.6% did not improve (Carlotti *et al* 1998). All cases were sensitive to marbofloxacin *in vitro*. This shows clearly that even in sensitive cases, oral antibiosis is unreliable as a sole therapy of otitis externa, but was helpful in about 70% of cases. Whether it speeds resolution compared with topical therapy alone in cases of otitis externa is unknown.

If there is not significant involvement of the pinna, the author does not use systemic antibiotics in these cases. The fundamental weakness of oral antibiotic medication in the treatment of otitis is its failure to penetrate to the surface of the ear canal and its lumen, where much of the infection resides, at sufficient concentrations to be effective. Other dermatologists have suggested their use in cases where there are neutrophils along with bacteria in cytological preparations, or persistent ulcerative changes in the canal on the grounds that it suggests that the bacterial infection is deeper seated in the ear (i.e. a folliculitis and/or furunculosis), or where there are significant proliferative changes in ears.

On the other hand, systemic antibiotics may well be indicated in the management of bacterial otitis media, depending on the case, if aggressive topical management is not possible. Where systemic antibiotics are to be used in cases of rod otitis, antibiotic selection should be based on a culture and *in vitro* sensitivity once cytology shows a homogenous (rather than mixed) population of rods present on cytology. Mixed bacteria tend to indicate a failure to control the microenvironment rather than an antibiotic failure (see below for details).

Some authors have recommended larger than doses of enrofloxacin up to 20 mg/kg daily for treatment of otitis. This recommendation is somewhat controversial in light of a study that examined the concentration of enrofloxacin in the ear tissue of cases with chronic end stage otitis. The results showed tissue concentrations of enrofloxacin to be consistently higher than plasma concentrations, and that in cases of *Pseudomonas* otitis sensitive to enrofloxacin, that dosing of 5mg/kg q24h should be sufficient to achieve effective tissue concentrations to kill the bacteria. However, in cases with intermediate or resistant *Pseudomonas* even dosing of 15-20 mg/kg of enrofloxacin daily would not reliably create high enough tissue levels to kill the bacteria (Cole *et al* 2009).

First line systemic anti-rod antibiotics:

- Base on culture and sensitivity results of an homogenous bacterial population. Culture of mixed bacterial populations is not recommended by this author. Note that most Australian labs now use moxifloxacin as a surrogate disk for enrofloxacin on sensitivity reports rather than ciprofloxacin.

Second line systemic anti-rod antibiotics:

- Consider performing MICs if available to enrofloxacin, marbofloxacin and ciprofloxacin to see if higher doses may be of benefit
- *In vitro*, ciprofloxacin (10-20mg/kg q24h) has shown better activity to *Pseudomonas* compared with enrofloxacin but sensitivity is not routinely done in many Australian labs any more. Its bioavailability is about half that of enrofloxacin so higher dosing is required.

Third line systemic anti-rod antibiotics

- Hospitalisation and use of IV ticarcillin has been reported. Use of IV tobramycin and amikacin may also be options but fluid therapy would be essential to minimise the risk of nephrotoxicity.

ANTIBIOTIC THERAPY FOR EARS WITH MAINLY COCCI ON CYTOLOGY

Aetiology

In Australia, the majority of cocci identified on culture are *Staphylococcus* (*pseud*)*intermedius* or β-haemolytic streptococci, the latter of which occur at about 25% of the frequency of *Staphylococcus*.

Diagnosis

In studies examining the correlation of cytology with otitis, high bacterial counts generally correlated well with clinical signs.

Cytology in normal dogs: <0.8 cocci per 1000x OIF
Cytology in dogs with otitis: >4 bacteria (rods or cocci) per 1000x OIF

Cytology in normal cats: <2 cocci per 3 1000x OIFs
Cytology in cats with otitis: >2.4 bacteria (rods or cocci) per 1000x OIF

Once again, this leaves a grey zone in cytology between normal and abnormal ears, and in all cases cytology should be considered in combination with clinical signs (or lack thereof) and examination of the ear before a diagnosis is made.

Topical Anti-Coccal Antibacterial Therapy

Disinfectants. Because of the generally good responsiveness of coccal infections to routine treatments, the author rarely uses disinfectants in these cases. Of the available commercial ear cleaners only EpiOtic (Virbac) EpiOtic (Virbac) bid x 14 days (68% resolution in a variety of infections but 80% still had mild-moderate ear exudate) has any proven activity for coccoid bacteria. Based on the ingredients, it would be expected that Milo's Ear Cleanser (Ceva-Delvet) and Ilium Oticlean (Ilium) would have some activity also but this has not been specifically reported. Use of a concurrent disinfectant would be recommended in the face of a resistant bacterial otitis where conventional therapy is not effective. Note than none of these products are middle ear safe. Tris EDTA, which is reported as not being ototoxic, is ineffective for cocci though Triz Plus (Dermapet) or just a 0.15% concentration of chlorhexidine solution (not scrub) may be beneficial and also reported middle ear safe.

Topical Antibiotics. The challenge for empirical therapy for cocci is the relative resistance of streptococci to some of the routine topical antibiotics, which otherwise tend to have reasonable activity for most *Staphylococcus* sp. For this reason products containing antibiotics with good efficacy against both bacteria are desirable. The authors first choice in this situation where the TM is intact is Canaural (Bayer) because of the combination of framycetin and fusidic acid. Other reasonable choices would be Otomax or Mometamax (Intervet Schering Plough) where both the gentamicin and clotrimazole have anti-coccal activity.

Where the TM is ruptured enrofloxacin is the only real choice, though its performance with streptococcal infections is less than stellar. If this was inadequate, then options include use of systemic therapies based on culture and sensitivity, and also ear wicks impregnated with more effective (but not middle ear safe) ointments.

Timentin, which has a spectrum of activity similar to clavulanic acid-amoxicillin with respect to cocci should be effective in the face of failure of other medications. If this is similarly ineffective it raises the possibility of a methicillin-resistant *Staphylococcus*. Culture and sensitivity should be performed at this stage to rule this possibility in or out, to help guide therapy (both systemically and topically) and also for human health considerations depending on the domestic situation of the owner. Other options in this situation that may be effective include chloramphenicol or clindamycin (see Appendix B).

First line topical anti-coccal antibiotics:

- TM intact: Canaural (Bayer) q12h best, consider also Otomax q12h or Mometamax q24h (Intervet Schering Plough)
- TM ruptured: enrofloxacin 1.5% with dexamethasone NaP depending on inflammation and middle ear safe vehicle (see Appendix C)

Second line topical anti-coccal antibiotics:

- TM intact: Timentin 6% q12h
- TM ruptured: ear wick placement with Canaural (Bayer) best, consider Mometamax (Intervet Schering Plough)

Third line topical anti-coccal antibiotics:

- Guided by culture and sensitivity results of an homogenous bacterial population

Systemic Anti-Coccal Antibacterial Therapy

The benefit of systemic antibiotic therapy in the management of bacterial otitis externa with cocci is also controversial and there are no studies looking at the efficacy of oral antibiotics in these cases with which to make any objective judgement. The author has experienced just once case of coccal otitis that responded to oral enrofloxacin as a sole therapy, amongst many that have not responded. This limited experience suggests again that oral antibiosis is probably unreliable as a sole therapy of coccal otitis externa, but may assist in some cases.

Similarly to *Pseudomonas* otitis, the author does not tend to use systemic anti-coccal antibiotics unless there is significant involvement of the pinna, a methicillin-resistant *Staphylococcus* was identified on culture and sensitivity or otitis media where aggressive topical management is not possible. Considerations for other dermatologists are the presence of neutrophils along with bacteria in cytological preparations, or persistent ulcerative changes in the canal suggestive of folliculitis and/or furunculosis, or where there are significant proliferative changes in ears.

Where systemic antibiotics are to be used in cases of coccal otitis, if there is any suspicion of resistance antibiotic selection should be based on a culture and *in vitro* sensitivity once cytology shows a homogenous (rather than mixed) population of cocci present on cytology. In the absence of this though, good empirical choices include cephalexin and clindamycin, which should be effective against both staphylococci and streptococci and both have good tissue penetration.

First line systemic anti-rod antibiotics:

- Cephalexin 22 mg/kg q12h, clindamycin 5-11mg/kg q12h

Second line systemic anti-rod antibiotics:

- Base on culture and sensitivity results of an homogenous bacterial population

ANTIBIOTIC THERAPY FOR EARS WITH MIXED INFECTION ON CYTOLOGY

Aetiology & Diagnosis

Mixed infections can contain upwards of six or more different rods and cocci, with or without *Malassezia*. They often return culture reports with phrases such as 'mixed skin flora'. At the lab they may try to pick some pathogens out of the microbial soup, and it is not impossible for significant bacteria such as *Pseudomonas* or *Staphylococcus* to be amongst the microbes present. Furthermore, less common bacteria such as *Enterococcus* may be present, and these may have disturbingly resistant antibiograms. Much like *Corynebacterium* though, there is no evidence that they are pathogenic when part of a mixed culture.

Mixed infections form when microenvironmental conditions in the ear are very much in favour of microbial growth, and so much so that just about anything grows there, including organisms that typically do not colonise the ear.

When these cases are identified on cytology, culture should be avoided as it is unrewarding at best and misleading at worst.

Topical Antibiotic Therapy

Bacterial resistance *in vivo* is rarely an issue in these cases as typically there has been no antibiotic pressure on the bacteria to become resistant, and most of the bacteria with innate resistance respond to improvement of the microenvironment, which is the key to management of these cases.

These ears need to be thoroughly cleaned and dried and inflammation managed if present. Use of an appropriate ear cleaner is directed towards what is most appropriate for microenvironmental management, rather than directed by infection management.

Empirical topical antibiotic therapy should be broad spectrum and directed towards the dominant morphological microbe if present. It is difficult to make a wrong choice so long as the microenvironment is controlled well. Challenges occasionally arise at recheck if the mixed population of organisms has become monomorphic with treatment. This may well suggest possible resistance to therapy, and the clinician is directed to the relevant section above in this instance.

First line topical mixed infection antibiotics:

- TM intact, mainly rods or yeast: Otomax q12h or Mometamax q24h (Intervet Schering Plough)
- TM intact mainly cocci: Canaural (Bayer) q12h
- TM intact numerous filamentous rods suggestive of anaerobes: Timentin 6% in propylene glycol (see Appendix C)
- TM not intact, yeast not present: enrofloxacin 1.5% q12h (see Appendix C)
- TM not intact, yeast present: Ear wick placement and one of the ointments above, in combination with oral ketoconazole 10mg/kg/day

Systemic Antibiotic Therapy

Systemic antibiotic therapy is typically not required with mixed infections with the exception noted above. The only other time it may be indicated is if the mixed infection becomes a monomorphic population of microbes. In that case, see the relevant section above.

APPENDIX A: SELECTED ANTIBIOTICS USED IN THE TREATMENT OF OTITIS

Amikacin

Mechanism of Action. Inhibit protein synthesis by binding to 30s ribosomal subunit. Entry into bacteria is oxygen dependent. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many cocci (*Staphylococcus*) and rods (*Klebsiella* spp., *Escherichia coli*, *Proteus, Pseudomonas aeruginosa*). Low efficacy against some cocci (streptococci). Ineffective against anaerobes.

Topical Ototoxicity. Yes.

Comments. Very broad activity veterinary aminoglycoside. Resistant to many of the bacterial enzymes that can inactivate other aminoglycosides. Consequently may be effective in tobramycin and gentamicin-resistant *Pseudomonas* strains. The antimicrobial activity of all aminoglycosides is enhanced in an alkaline environment, and activity is poor in an acid environment. If acidifying cleansers are used in conjunction with aminoglycosides, the products should be applied at least 1 hour apart. Not available as a commercially produced topical product, but the injectable product (Amikin, Bristol-Meyers Squibb, 500mg/mL) has been diluted to a concentration of 30 to 50 mg/mL (in sterile saline or tris EDTA) by veterinarians for topical use.

Ciprofloxacin

Mechanism of Action. Inhibition of DNA gyrase. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many rods (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Proteus*) and cocci (*Staphylococcus*). Variable activity against streptococci. Ineffective against anaerobes.

Topical Ototoxicity. None reported.

Comments. Systemic use contraindicated in growing dogs. Bioavailability is half that of oral enrofloxacin. Although resistance of *P. aeruginosa* to ciprofloxacin has been reported to be less common than to enrofloxacin, there are also several laboratory-dependent explanations for the discrepancy that may prove it technical rather than clinical. The oral dose is 10-20mg/kg once daily. Concentrated in inflammatory cells. Note that many labs in Australia previously used ciprofloxacin disks as surrogate disks for enrofloxacin in susceptibility testing, but this has now been replaced by marbofloxacin.

Cephalexin

Mechanism of Action. Inhibition of bacterial cell wall synthesis. Bactericidal. Time dependent.

Spectrum of Activity. Effective for cocci (Staphylococcus, streptococcus). Reasonable efficacy for some rods (*Klebsiella* spp., *Escherichia coli*, *Proteus*). Variable efficacy against anaerobes.

Topical Ototoxicity. None reported but not recommended.

Comments. Chiefly used as an adjunctive oral therapy for otitis media or severe otitis externa involving mainly cocci where culture indicates sensitivity to cephalexin. Tissue penetration is good. Topical use of the injectable formulation has not been reported.

Clavulanic Acid – Amoxicillin

Mechanism of Action. Inhibition of bacterial cell wall synthesis. Bactericidal. Time dependent.

Spectrum of Activity. Effective for cocci (*Staphylococcus*, *Streptococcus*). Generally good efficacy for some rods (*Klebsiella* spp., *Escherichia coli*, *Proteus, Corynebacterium*). Good efficacy against anaerobes. Not effective against *Pseudomonas*.

Topical Ototoxicity. None reported but not recommended.

Comments. Chiefly used as an adjunctive oral therapy for otitis media or severe otitis externa involving mainly cocci where culture indicates sensitivity to clavulanic acid-amoxicillin. Topical use of the injectable or oral suspension formulation has not been reported.

Clindamycin

Mechanism of Action. Inhibition of protein biosynthesis. Binds to the ribosomal 50S subunit. Clindamycin is primarily bacteriostatic, but may be bactericidal at high concentrations, and more so with anaerobes. Time dependent.

Spectrum of Activity. Effective for cocci (Staphylococcus, streptococcus). Ineffective against aerobic rods. Excellent efficacy against anaerobes.

Topical Ototoxicity. None reported but not recommended.

Comments. Chiefly used as an adjunctive oral therapy for otitis media or severe otitis externa involving mainly cocci where culture indicates sensitivity to clindamycin. Anecdotally, it has been used successfully orally as a sole therapy for otitis media in a cat. Topical use of the oral suspension formulation has not been reported but given it contains alcohol is not recommended for use if the TM is ruptured. Higher dosing (11mg/kg q12h) may be more appropriate for inflammatory otitis media.

Chloramphenicol

Mechanism of Action. Inhibition of protein biosynthesis. Binds to the ribosomal 50S subunit. Chloramphenicol is primarily bacteriostatic, but may be bactericidal at high concentrations, and more so with anaerobes. Time dependent.

Spectrum of Activity. Effective for cocci (Staphylococcus, streptococcus). Variable efficacy against aerobic rods (*E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas*) . Good efficacy against anaerobes.

Topical Ototoxicity. Yes.

Comments. The only real indication for use of this drug is for infections involving multi-resistant *Staphylococcus* sp. where culture and sensitivity indicates no other options. Oral formulations and 1% topical ophthalmic formulations are available. Chloramphenicol is active at a wide range of pH so no particular restrictions apply to ear cleaner pH. It is known to be associated with aplastic anaemia in human beings, and concern over potential drug exposure to the pet owner should limit its routine use. Prolonged systemic exposure may cause dose related bone marrow suppression in the patient.

Enrofloxacin

Mechanism of Action. Inhibition of DNA gyrase. Bactericidal. Concentration dependent.

Bacterial Activity. Effective for many rods (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Proteus*) and cocci (*Staphylococcus*). Variable activity against streptococci. Ineffective against anaerobes.

Topical Ototoxicity. None reported.

Comments. May rarely cause blindness in cats when used systemically, chiefly at doses >5mg/kg/day. Systemic use contraindicated in growing dogs. Bacterial resistance is known to occur by rapid mutation, especially in the presence of subtherapeutic concentrations. With systemic administration 30-40% of enrofloxacin is converted to ciprofloxacin. There is no conversion to ciprofloxacin with topical administration. Concentrated in inflammatory cells. Note that many labs in Australia use marbofloxacin surrogate disks for enrofloxacin in susceptibility testing. Ideal pH for maximum lipophilicity (and therefore bacterial penetration) is approximately pH 7 or higher. Activity in acidic environments may be somewhat reduced. If acidifying cleansers are used in conjunction with enrofloxacin topically, the products should be applied at least 1 hour apart.

Framycetin

Mechanism of Action. Inhibit protein synthesis by binding to 30s ribosomal subunit. Entry into bacteria is oxygen dependent. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many rods (*Klebsiella* spp., *Escherichia coli*, *Proteus*) and cocci (*Staphylococcus*). Variable activity against *Pseudomonas aeruginosa*, streptococci. Ineffective against anaerobes.

Topical Ototoxicity. Yes.

Comments. Generally less active than gentamicin with respect to gram negative organisms. *In vitro* sensitivity of *Pseudomonas* sp. to framycetin does not translate well to clinical efficacy in the author's experience. The antimicrobial activity of all aminoglycosides is enhanced in an alkaline environment, and activity is poor in an acid environment. If acidifying cleansers are used in conjunction with aminoglycosides, the products should be applied at least 1 hour apart. Note that many labs in Australia use neomycin disks as surrogate disks for framycetin in susceptibility testing.

Fusidic Acid

Mechanism of Action. Bacterial protein synthesis inhibitor by preventing the turnover of elongation factor G (EF-G) from the ribosome. Bacteriostatic.

Spectrum of Activity. Effective for many cocci (*Staphylococcus*, streptococci) and *Corynebacterium*. No activity against other aerobic rods. Some efficacy against anaerobes.

Topical Ototoxicity. Yes.

Comments. Combination with other antibiotics (including framycetin) can prevent development of resistance by staphylococci, which is a risk with monotherapy. Fusidic acid should not be used with quinolones, with which they are antagonistic. Can remain effective for methicillin-resistant staphylococci.

Gentamicin (Aminoglycoside)

Mechanism of Action. Inhibit protein synthesis by binding to 30s ribosomal subunit. Entry into bacteria is oxygen dependent. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many rods (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Proteus*) and cocci (*Staphylococcus*). Variable to poor activity against streptococci. Ineffective against anaerobes.

Topical Ototoxicity. Yes, in laboratory animals, but an aqueous formulation 3mg/mL has been used topically bid up to 21 days in dogs with ruptured TMs with no adverse reactions (Strain et al 1995).

Comments. Gentamicin topically can be inactivated by organic debris so a clean ear is mandatory. The antimicrobial activity of all aminoglycosides is enhanced in an alkaline environment, and activity is poor in an acid environment. If acidifying cleansers are used in conjunction with aminoglycosides, the products should be applied at least 1 hour apart.

Gramicidin

Mechanism of Action. Increases permeability of the cell wall leading to osmotic damage. Bactericidal.

Spectrum of Activity. Effective for cocci. No efficacy against rods. Good efficacy against Gram positive anaerobes.

Topical Ototoxicity. Yes.

Comments. -

Marbofloxacin (Fluoroquinolone)

Mechanism of Action. Inhibition of DNA gyrase. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many rods (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Proteus*) and cocci (*Staphylococcus*). Variable activity against streptococci. Ineffective against anaerobes.

Topical Ototoxicity. None reported.

Comments. Systemic use contraindicated in growing dogs. Reported effective to some strains of *Pseudomonas* resistant *in vitro* to enrofloxacin and ciprofloxacin. Concentrated in inflammatory cells. Not current available as a topical formulation in Australia. Note that many labs in Australia use marbofloxacin surrogate disks for enrofloxacin in susceptibility testing.

Neomycin

Mechanism of Action. Inhibit protein synthesis by binding to 30s ribosomal subunit. Entry into bacteria is oxygen dependent. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many cocci (*Staphylococcus*). Variable activity against some rods (*Klebsiella* spp., *Escherichia coli*, *Proteus,* rarely *Pseudomonas aeruginosa)* and some cocci (streptococci). Ineffective against anaerobes.

Topical Ototoxicity. Yes.

Comments. Generally less active than gentamicin with respect to gram negative organisms. The antimicrobial activity of all aminoglycosides is enhanced in an alkaline environment, and activity is poor in an acid environment. If acidifying cleansers are used in conjunction with aminoglycosides, the products should be applied at least 1 hour apart. Note that many labs in Australia use neomycin disks as surrogate disks for framycetin in susceptibility testing. Relatively common cause of topical drug eruption.

Polymyxin B

Mechanism of Action. Cationic surface-active agents that increase permeability of the bacterial cell membrane via chelation of membrane phospholipid components (a detergent-like action), leading to osmotic damage. Bactericidal.

Spectrum of Activity. Effective for some rods (*Pseudomonas aeruginosa*). Variable efficacy for some rods (*Klebsiella* spp., *Escherichia coli*). Poor *in vitro* efficacy for *Proteus*. No efficacy against Gram positive cocci. Minimal efficacy against anaerobes.

Topical Ototoxicity. Yes.

Comments. Has a synergistic effect *in vitro* with miconazole against *Escherichia coli, Pseudomonas aeruginosa*, and *Malassezia pachydermatis.* Rapidly inactivated by organic debris. Tends to reduce inflammation induced by endotoxin components of Gram negative bacterial cell walls. The concentration in Surolan is about 50% of that anecdotally used by US dermatologists (10000IU/mL) and this may explain the author's experience of this antibiotic in the treatment of *Pseudomonas* infections not matching good *in vitro* sensitivities, in contrast to the US dermatologist experience.

Silver Sulphadiazine

Mechanism of Action. Impairment of DNA replication and bacterial cell wall damage, leading to osmotic changes. Bactericidal.

Spectrum of Activity. Effective for many cocci (*Staphylococcus* inc. methicillin-resistant, streptococci) and rods (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Proteus*) Good efficacy against anaerobes. Low efficacy against *Malassezia pachydermatis.*

Topical Ototoxicity. Anecdotally not, but no evidence for or against.

Comments. Reduces MIC of *Pseudomonas* for enrofloxacin when used concurrently. May help healing of ulcerated ear canals.

Thiostrepton

Mechanism of Action. Inhibits proteins synthesis by binding to 50S ribosomal subunit. Bacteriostatic.

Spectrum of Activity. Effective for cocci. Variable efficacy for rods.

Topical Ototoxicity. Unknown.

Comments. -

Ticarcillin - Clavulanic Acid

Mechanism of Action. Inhibition of bacterial cell wall synthesis. Bactericidal. Time dependent.

Spectrum of Activity. Effective for cocci (*Staphylococcus*, *Streptococcus*), some rods (*Pseudomonas, Corynebacterium)* and anaerobes. Moderate activity against some rods (*Klebsiella* spp., *Escherichia coli*, *Proteus*)

Topical Ototoxicity. Yes (hearing loss)

Comments. Available commercially as Timentin (GlaxoSmithKline). Used as a 6% solution (see appendix C for formulation) twice daily. Stable for at least 30 days refrigerated. Low pH or presence of free metal ions may inactivate – concurrent use of Tris-EDTA should avoid this.

Tobramycin

Mechanism of Action. Inhibit protein synthesis by binding to 30s ribosomal subunit. Entry into bacteria is oxygen dependent. Bactericidal. Concentration dependent.

Spectrum of Activity. Effective for many cocci (*Staphylococcus*) and rods (*Klebsiella* spp., *Escherichia coli*, *Proteus, Pseudomonas* *aeruginosa*). Low efficacy against some cocci (streptococci). Ineffective against anaerobes.

Topical Ototoxicity. Yes.

Comments. Very broad activity veterinary aminoglycoside. More active against *Pseudomonas*, including about two thirds of gentamicin-resistant strains. May be used concurrently with Timentin 6% solution. The antimicrobial activity of all aminoglycosides is enhanced in an alkaline environment, and activity is poor in an acid environment. If acidifying cleansers are used in conjunction with aminoglycosides, the products should be applied at least 1 hour apart. The injectable product (40mg/mL injectable, several manufacturers) has been diluted to a concentration of 8mg/mL (in sterile saline) for otic use. Long-term stability (>1 week) of the diluted injectable formulation is unknown. It is also available as a 3mg/mL ophthalmic preparation in Australia (Tobrex, Alcon Laboratories).

APPENDIX B: SELECTED ANTIFUNGALS USED IN THE TREATMENT OF OTITIS

Clotrimazole

Mechanism of Action. Azole antifungal. Causes disruption of cell wall ergosterol biosynthesis via P450 enzyme inhibition. Fungistatic, though concentrations > 10µg/mL are reported fungicidal.

Spectrum of Activity. Effective for *Malassezia*, *Candida*, dermatophytes, filamentous fungi including *Aspergillus*, dimorphic fungi, Gram positive cocci (*Staphylococci*, *Streptococci*).

Topical Ototoxicity. No.

Comments. Studies show generally good *in vitro* efficacy against *Malassezia*, showing variably a potency equivalent to nystatin and less than miconazole, to significantly more than both these other drugs. Regional variation in strain susceptibility has been suggested to explain this. Clinical failure to respond has been noted occasionally by the author in cases of yeast otomycosis, and *in vitro* resistance demonstrated in some of these cases, suggesting failure in other cases may have a pharmacological basis.

Fluconazole

Mechanism of Action. Azole antifungal. Causes disruption of cell wall ergosterol biosynthesis via P450 enzyme inhibition. Fungistatic. Time dependent.

Spectrum of Activity. Effective for *Malassezia*, most *Candida*, some dermatophytes, variably *Aspergillus*, some dimorphic fungi.

Topical Ototoxicity. No.

Comments. Dose range is 2.5-10mg/kg daily. Dosing with food is not required. Side effects include nausea, vomiting, inappetance. Does not affect hormone synthesis. P450 inhibition causes significant interactions with numerous drug P450 substrates including cyclosporin and phenobarbitone. Has extremely high concentrations in the stratum corneum and sweat, with higher amounts of free drug than highly protein bound itraconazole. While less active *in vitro* against *Malassezia* than other azoles, its higher free drug availability at the surface of the skin and cerumen may counteract this *in vivo*. However, its use for yeast otomycosis is not well reported. Available now in several generic brands in 50-

200mg capsules but still expensive. Compounded formulations have good oral bioavailability.

Itraconazole

Mechanism of Action. Azole antifungal. Causes disruption of cell wall ergosterol biosynthesis via P450 enzyme inhibition. Fungistatic..

Spectrum of Activity. Effective for *Malassezia*, most *Candida*, some dermatophytes, variably *Aspergillus*, some dimorphic fungi.

Topical Ototoxicity. No.

Comments. Dose 5mg/kg q24h (dogs) 10 mg/kg q24h (cats). A study in dogs found no significant clinical difference in response between daily administration and twice weekly administration in the treatment of *Malassezia* dermatitis and otitis externa. It is unreliable as a sole therapy in the treatment of yeast otitis externa. Itraconazole should be administered with food; the concurrent administration of antacids, H2-blockers, and cholinergics is contraindicated. It has greater potency, decreased toxicity, and a wider spectrum of activity compared with ketoconazole. Does not alter hormone levels. Side effects include nausea, vomiting, inappetance, and hepatopathy. P450 inhibition causes significant interactions with numerous drug P450 substrates including cyclosporin and phenobarbitone though less than ketoconazole. Has extremely high concentrations in the sebum followed by the stratum corneum which persist following cessation of therapy. A severe, dose-related ulcerative dermatitis secondary to vasculitis has been seen in 5-10% of dogs given 10 mg/kg doses of itraconazole. If the condition is identified early, drug withdrawal leads to resolution; if not recognized early, severe, extensive necrosis and sloughing can develop. Available as 100mg capsules (Sporanox, Janssen) which can be resized so long as the granules remain intact. Compounded formulations should be avoided due to poor bioavailability. Use of 1% oral itraconazole elixir (Sporanox Oral Solution) topically has also been reported. Although sticky (in a syrup base), the product was effective.

Ketoconazole

Mechanism of Action. Azole antifungal. Causes disruption of cell wall ergosterol biosynthesis via P450 enzyme inhibition. Fungistatic.

Spectrum of Activity. Effective for *Malassezia*, most *Candida*, dermatophytes, filamentous fungi including some *Aspergillus*, dimorphic fungi.

Topical Ototoxicity. No.

Comments. Dosed orally in dogs at least 10mg/kg q24h for otomycosis, and up to 20mg/kg q12h has been reported. Must be dosed with food. The author has been underwhelmed by the response in yeast otomycosis cases at 5mg/kg q24h. Side effects include nausea, vomiting, elevations in liver values, and rarely hepatopathy. High doses may have an adverse effect on testosterone or cortisol production. P450 inhibition causes significant interactions with numerous drug P450 substrates including cyclosporin and phenobarbitone. Systemic excretion in sweat glands may mean that with systemic dosing, it accumulates better in the ear canal than itraconazole. In humans, drug levels persist in the skin and nails for some weeks after therapy ceases. Available as Nizoral (Janssen) 200mg tablets. The author has used compounded ketoconazole 2% in squalene suspension for topical use in a single case of yeast otomycosis in the presence of a ruptured TM.

Miconazole

Mechanism of Action. Azole antifungal. Causes disruption of cell wall ergosterol biosynthesis via P450 enzyme inhibition. Fungistatic.

Spectrum of Activity. Effective for *Malassezia*, *Candida*, dermatophytes, filamentous fungi including *Aspergillus*, dimorphic fungi, Gram positive cocci (*Staphylococci*, *Streptococci*).

Topical Ototoxicity. No.

Comments. Studies show variable efficacy against *Malassezia*, variably showing potency both more or less than that of clotrimazole. Regional variation in strain susceptibility has been suggested. Clinical failure to respond has been noted occasionally by the author in a single case of yeast otomycosis, and *in vitro* resistance demonstrated in this cases. Miconazole has a synergistic effect *in vitro* with polymyxin B against *Escherichia coli, Pseudomonas aeruginosa*, and *Malassezia pachydermatis.*

Nystatin

Mechanism of Action. Polyene antifungal. Binds to sterols in the fungal cell membrane, thereby altering permeability and mediating cell death by osmotic destruction. Fungicidal at 4 times MIC.

Spectrum of Activity. Effective for *Malassezia*, some *Candida*, dermatophytes, some filamentous fungi, some dimorphic fungi.

Topical Ototoxicity. No.

Comments. Useful anti-yeast product. Most studies find it less potent *in vitro* compared with the azoles but clinical resistance has been rarely been documented, and not at all by the author.

Terbinafine

Mechanism of Action. Allylamine antifungal. Inhibition of squalene epoxidase leads to disruption of ergosterol biosynthesis and cell wall damage.

Spectrum of Activity. Effective for *Malassezia*, *Candida*, dermatophytes, filamentous fungi, dimorphic fungi.

Topical Ototoxicity. Unknown.

Comments. Dose 30 mg/kg q24h orally. Terbinafine in humans is not found in sweat and is thought to diffuse to back diffuse to the stratum corneum from sebum. Its use for *Malassezia* otitis is not well reported. 1% solution (Lamisil) has been used successfully in a single patient. However, at this time it is only available as a cream or spray in Australia.

APPENDIX C: SELECTED COMPOUNDED EAR FORMULATIONS

Enrofloxacin (20mL)

- 6mL Baytril Injectable 50mg/mL (for a final concentration of 15mg/mL enrofloxacin)
- 14mL vehicle, **or**
- 13.6mL vehicle with 0.4mL 5% dexamethasone NaP (for a final concentration of 1mg/mL dexamethasone NaP), **or**
- 12mL vehicle with 2mL 5% dexamethasone NaP (for a final concentration of 5mg/mL dexamethasone NaP)

The vehicle used may be saline or propylene glycol. Enrofloxacin tends to precipitate in Methopt tears and as such this is not recommended as a vehicle. Stability in other vehicles is untested but the authors clinical impression is that they remains effective for at least 2 weeks. Vehicles aside from propylene glycol have not been reported to be ototoxic and should be safe in the face of a ruptured tympanic membrane. Store refrigerated.

Timentin 6% (24mL)

- To make the stock concentrate, add 6mL sterile water for injection to the bottle of 3.1g Timentin (GlaxoSmithKline) and shake until dissolved. Add a further 6.9mL of sterile water and shake well. This is the 24% stock solution and may be frozen in 6mL aliquots. This solution should be stable for approximately 6 months.

To make the ear drops, use:

- 6mL of the 24% stock solution and add to this
- 18mL vehicle, **or**
- 17.52mL vehicle and 0.48mL 5% dexamethasone NaP (for a final concentration of 1mg/mL dexamethasone NaP), **or**
- 15.6mL vehicle and 2.4mL 5% dexamethasone NaP (for a final concentration of 5mg/mL dexamethasone NaP)

The vehicle used may be saline, Methopt Tears (hypromellose), or propylene glycol. Stability testing with saline found the 6% solution stable for at least one month when refrigerated. Vehicles aside from propylene glycol have not been reported to be ototoxic and should be safe in the face of a ruptured tympanic membrane. Store refrigerated.

Enrofloxacin and Triz EDTA (118mL)

- Triz EDTA 118ml bottle of dried powder, and add to this
- 23.6mL Baytril Injectable 50mg/mL (for a final concentration of 10mg/mL enrofloxacin)
- 94.4 mL distilled water, **or**
- 92.04mL distilled water with 2.36 mL 5% dexamethasone NaP (for a final concentration of 1mg/mL dexamethasone NaP), **or**
- 82.6mL vehicle with 11.8mL 5% dexamethasone NaP (for a final concentration of 5mg/mL dexamethasone NaP)

Stability is untested but all medications should remain stable at room temperature.

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Table 12.1. Selected Commercial Otic Preparations Available in Australia

Product	Manufacturer	Active Ingredients	Vehicle	Author comments
Otomax Ointment	Intervet Schering Plough	Gentamicin 3 mg/mL Betamethasone 1 mg/mL Clotrimazole 10 mg/mL	Mineral oil-based system containing a plasticised hydrocarbon gel	**Best cytological indications**: Mixed infections, predominantly yeast infections with rods or cocci **Limitations**: Clotrimazole resistant *Malassezia pachydermatis* have been identified by the author, and occasional clotrimazole non-responding yeast otitides have been identified anecdotally by other dermatologists (Kennis 2007, Morris 2004). Gentamicin is inactivated by purulent exudate and organic debris, so control of inflammation and exudate is mandatory for best performance in ears with bacterial otitis. Prolonged dosing or overly generous dosing can lead to a 'greasy' ear with sterile folliculitis on the pinna. **Other:** Clotrimazole may be active against streptococci that gentamicin misses.
Mometamax Ointment	Intervet Schering Plough	Gentamicin 3 mg/mL Mometasone furoate 1 mg/mL Clotrimazole 10 mg/mL	Mineral oil-based system containing a plasticised hydrocarbon gel	**Best cytological indications**: Mixed infections, predominantly yeast infections with rods **Limitations**: Once daily therapy seems a little less efficacious for yeast treatment compared with Otomax. Clotrimazole resistant *Malassezia pachydermatis* have been identified by the author, and occasional clotrimazole non-responding yeast otitides have been identified anecdotally by other dermatologists (Kennis 2007). Gentamicin is inactivated by purulent exudate and organic debris, so control of inflammation and exudate is mandatory for best performance in ears with bacterial otitis. **Other:** Mometasone is a potent glucocorticoid and useful for aggressive topical reduction of inflammation. Once daily registration improves compliance and reduces occlusive folliculitides and maceration. Clotrimazole may be active against streptococci that gentamicin misses.
Canaural Compositum Suspension	Bayer Australia Ltd (Animal Health)	Fusidic acid 4.6mg/mL Framycetin 4.6 mg/mL Nystatin 92000 IU/mL (approx 18mg/mL) Prednisolone 2.3 mg/mL	Sesame oil	**Best cytological indications**: Predominantly cocci; yeast infections non-responsive to azoles **Limitations**: Variable efficacy for common otic rods, and seems less effective *in vivo* for *Pseudomonas* than *in vitro* sensitivity would suggest. Leaves residue in ear canals that may be present for weeks to months after treatment finishes. **Other:** The powder-in-oil form of this medication may contribute pharmacokinetically to its good *in vivo* anti-yeast performance. Has 2 anti-coccal ingredients.

Surolan Suspension	Ausrichter Pty Ltd	Polymyxin B sulphate 0.529 mg/mL Prednisolone acetate 5 mg/mL Miconazole nitrate 23 mg/mL	Liquid paraffin	**Best cytological indication**: Predominantly yeast with some cocci **Limitations**: Is ineffective for *Proteus*, which is present in about 10% of cases submitted for culture in Australia., and there are high levels of polymyxin resistance also for *E. coli*. May be useful in specific cases of *Pseudomonas* but polymixin sensitivity to organic debris means ears must be very clean and inflammation well controlled. The author strongly prefers other choices in these cases. *Malassezia pachydermatis* resistance to miconazole has been positively identified in one case by the author. **Other:** The paraffin vehicle is useful for breaking up small amounts of cerumen.
Baytril Otic Antibacterial Drops	Bayer Australia Ltd (Animal Health)	Enrofloxacin 5 mg/mL Silver sulfadiazine 10mg/mL	1.0% w/v benzyl alcohol (as a preservative) and cetylstearyl alcohol (as a stabilizer) in a neutral oil and purified water emulsion	**Best cytological indications**: Mixed bacterial infections, *Pseudomonas* infections where the addition of silver sulfadiazine is desirable **Limitations**: Silver sulfadiazine shows only weak activity for yeast. The lack of a topical glucocorticoid means that for cases where inflammation is present, oral glucocorticoids will be required. Alternatively, 2.36mL of 5% dexamethasone NaP can be added to the 115.64mL of distilled water when reconstituting Triz-EDTA if this is being used concurrently.
Panalog Ointment	Novartis Animal Health Australasia Pty Ltd	Neomycin sulphate 2.5 m/g/mL Nystatin 100000 IU/mL (approx. 20mg/mL) Thiostrepton 2500 IU/mL Triamcinolone acetonide 1 mg/mL	Plastibase (mixture of 5% polyethylene and 95% mineral oil)	**Best cytological indication:** Predominantly cocci, some yeast **Limitations:** In a comparative study it performed worse than Surolan in ears with predominantly *Malassezia* otitis. Neomycin and thiostrepton are not reliable for many rods. There are better choices for most situations.

NOTES:

Chapter 13

Ear Cleaning Techniques

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INTRODUCTION: THE PHILOSOPHY OF EAR CLEANING

While much has been published on the topic of cleaning ears, there is very little evidence-based medicine on the subject, which means an approach to the topic is going to be inherently a subjective one. The lack of evidence-based medicine is not surprising. The variation in ear canals (size, shape, chronicity of disease), nature of otic exudate (cerumen, serum, inflammatory cells, keratinocytes, water, residual medications previously used), ear cleaning technique and skill level of the person performing the cleaning makes standardisation and meaningful comparisons of products and techniques nearly impossible.

Fortunately, the end result of ear cleaning is less ambiguous – an ear is either clean or it is not by time the cleaning process is finished. Any ear cleaning technique that successfully cleans an ear with no, or at least minimal, adverse effect on the patient, and which is practical for the client and veterinarian, is a valid ear cleaning technique.

What follows is the author's opinions and experiences on the topic, coloured by other dermatologists' published opinions and wherever possible, evidence-based medicine.

WHY IS EAR CLEANING NECESSARY?

There are numerous reasons why some infected ears continue to quickly relapse or fail to respond to medications. In the author's experience the #1 reason for ears failing to respond as expected to therapy is a failure to adequately clean the ear. This is because ear exudate:

- can make the otic microenvironment more favourable for the growth of micro-organisms (e.g. *Malassezia* feed on lipids in wax, purulent exudate further increases inflammation and moisture of ears making it more favourable for *Pseudomonas spp.*)

- inhibits penetration of medication, leading to ongoing untreated infections in the deep aspect of the ear canals
- inactivates some medications (e.g. purulent exudate inactivation of gentamicin or polymixin B)
- contributes to irritation and pain.

Because of this, a clean ear is already halfway to being cured. However, it is important to note that not all infected ears will need cleaning. Many mild and sometimes more moderate infections respond well to routine topical ointments without adjunctive cleaning as the vehicles of these can often dissolve small amounts of exudate.

So two important questions then arise:

1. When does an ear need cleaning?
2. What is the most appropriate way to clean a problem ear?

WHEN TO CLEAN AN EAR

This is the easier of the two issues. For initial treatment of a problem ear, the rule is simple: ear cleaning should be considered in all cases whenever the ear drum cannot be visualised. This is because if there is enough exudate to block visualisation of the ear drum, then there is enough to prevent penetration of the medication to treat the full length of the ear canal. Alternatively, if the ear drum cannot be visualised because the canal is stenotic or the dog is noncompliant, then general anaesthesia (GA) and flushing if required should be considered to make sure that the cause for the ear infection is not persisting in the deep aspect of the canal, and that the ear drum is not ruptured (which would limit the kinds of medications able to be safely used).

MAKING A DECISION: OPTIONS FOR EAR CLEANING

There are only two practical general options for ear cleaning in the dog: chemical cleaning with ear cleaners or physical cleaning. By the latter term, the author means general anaesthesia (GA) and flushing rather than conscious flushing using devices such as the Auriclean (which he has found less than satisfactory compared with other options) or flushing under sedation. Sedation alone is inadequate for a vast majority of cases as it is not sufficient for close cleaning of the deep ear canal where any movement of the head risks iatrogenic perforation of the ear drum. It is also possible that vigorous struggling may lead to avulsion injuries of the ear canal in unsedated or poorly sedated animals being flushed.

Thus, for severely affected ears, flushing under GA is by far the method of choice but consideration always needs to be given to case selection. In practice, it may not be medically appropriate or financially viable for cleaning to be performed in this way. Ear cleaners are initially cheaper to use and effective in specific cases but case selection is also critical for best success. It is important to realise the perceived initial economy of using ear cleaners over a GA and ear flush can rapidly be eroded by lack of success and multiple ear revisits. The author's practice sees many cases that could have been quickly resolved with GA and ear flushing initially with appropriate medication that otherwise drag on for months and in some cases years.

Important for any sort of ear cleaning though is a workable ear canal. Severe stenosis will limit both the efficacy of chemical or physical ear cleaning and this must be addressed if possible prior to cleaning. Inflammatory or epithelial hypertrophic stenosis will often respond to aggressive systemic, topical or intra-mural glucocorticoid use BUT if stenosis is cause by glandular hypertrophy, scarring, polyps or neoplasia then medical management of the case may not be possible and surgery in these cases may be the only real option. The take home message here is simply that if the ear canal and tympanic membrane (TM) are structurally intact, then the ear will respond to appropriate medical therapy. If there are uncorrectable structural defects in the ear canal, then surgery is likely to be required.

The pros and cons of each approach to ear cleaning are summarised in Table 13.1 below. Clients need to know these to make an informed decision, especially when it comes to the increased initial cost of a GA and flush.

Table 13.1. Pros and Cons of Ear Cleaning Methods

PROS	CONS
GA and Ear Flush	
• much better visualisation of the ear canal (and any anatomical abnormalities that may be contributing to the problem) • removal of foreign bodies if present • close examination of the patency of the ear drum and thus avoidance of any ototoxic substances if perforated • much more rapid removal of exudate • removal of exudate that simply is not possible by other means (such as deep compacted keratinous plugs)	• GA required • higher initial cost • equipment requirements • skill requirements
Ear Cleaners	
• effective removal of exudate in specific cases • cheap • no GA required	• dependent on client compliance • use in ears where ear drum cannot be observed carries risk of ototoxicity with most products if ear drum is perforated. (Note Triz EDTA (Dermapet) has no evidence for being ototoxic.) • all are ineffective with certain exudates (e.g. compacted keratin) • some products are more effective than others depending on the type of exudate present • limited efficacy where significant amounts of hair are matted in the ear • some products can be irritant, esp. with an inflamed ear • rarely able to remove foreign bodies if present

THE NATURE OF CANINE EAR EXUDATE: KNOW THE ENEMY

Canine ear exudate is far from a consistent composition, and makes rational selection of ear cleaners challenging. Cytology can assist with determination of the composition of the exudate in combination with gross examination.

Keratinocytes

Like any other keratinising epithelium in the body, the ear canal steadily exfoliates keratinocytes into the lumen of the ear canal. These cells are normally picked up in the cerumen and transported to the entrance of the ear canal. When the self cleaning mechanism fails, keratinocytes can compact into tight plugs (keratoliths), typically in the deeper aspect of the ear canal. It is not uncommon in ears with chronic otitis to have a ceruminous or purulent exudate in the vertical canal, which becomes more keratinous in the deeper horizontal canal. In ears that have become chronically wet (macerated) because of medications or inflammation, keratinocytes can be shed in sheets from the canal wall, and form a sticky, ‘Clag’ glue-like creamy exudate that is difficult to remove. Neutrophils with or without microbes may also be present in severely macerated ears.

Cerumen

Cerumen is primarily made up of fatty acids produced by modified apocrine (ceruminous) glands and sebaceous glands lining the ear canal. Its consistency in normal dogs can vary between individuals, and looking at the fatty acid composition and total fatty acid content of cerumen in dogs with *Malassezia* otitis, there is significant breed variation. The water content of cerumen may be higher in dogs with otitis. Grossly, exudate which is mainly fatty acids should be somewhat waxy and crumbly. This would be softer with a higher water content. In cases where the self cleaning mechanism fails (either permanently or transiently after an episode of acute otitis), discrete wax balls (ceruminoliths) can form in the horizontal canal. Ceruminoliths will have varying quantities of keratinocytes within them, and the greater the quantity of keratinocytes within the ceruminolith, the more resistant they tend to be to ceruminolytic ear cleaners.

Certain diseases (e.g. sebaceous adenitis) may lead to a deficiency in cerumen production, and this can lead to a failure of self cleaning, with accumulation of shed keratinocytes in the ear canal.

Purulent Exudate

Purulent exudate is composed of inflammatory cells and protein-rich serum. It is commonly associated with ear canal erosion and ulceration. Purulent exudates tend to be tenacious because of the protein, and somewhat resistant to removal. It is low in fats (making ceruminolytics largely useless) and is commonly associated with maceration of the canal. Purulent exudate concurrent with cerumen leads to a slimy dark exudate.

CHEMICAL EAR CLEANING: USE OF EAR CLEANERS

Selection of the most appropriate ear cleaner for any given case is a difficult issue where several different factors need to be considered. Ear cleaners do not just clean (with variable efficacy depending on the cleaner and the exudate) but they also have antimicrobial activities and physical properties (such as drying or pH alteration), and for any given case the clinician needs to be clear in his or her mind what the main rationale for their use is so as to best achieve a positive outcome. Table 13.2 lists currently available ear cleaners in Australia and their recommended uses according to the author.

Removing Exudate

Few studies have examined ear cleaners' ability to clean ears. This limitation is further compounded by the lack of standardisation in the types of exudate a dog's ear can produce, making direct comparisons between products difficult. For this reason, the author conducted an *in vitro* study with others examining the performance of various ear cleaning products against a standardised synthetic canine cerumen.

In this study, 2ml of ear cleaner and approximately 2g of synthetic wax was placed in a test tube. The test tube was then placed in an agitating water bath at 35ºC for 20 minutes, before being inverted and drained to allow any dissolved wax to run out. The process was repeated for a total of 5 times. This was designed to simulate home usage of the test products. The remaining wax was then weighed and the amount removed calculated. Tested products from the Australian market included Epi-Otic (Virbac), Bayer Clean Ear Solution (Bayer), Leo Ear Cleaner (Boehringer Ingelheim, no longer on the market), Malacetic and Malacetic AP (Dermapet), Malaseb Shampoo (Dermcare) diluted 1:30, Ilium Otoclean (Troy Laboratories), a compounded alcoholic product based on Leo Ear Cleaner, Milo's Ear Cleaner (CEVA-Delvet), Triz EDTA (Dermapet) and neat propylene glycol (Cattlekare). PAW Gentle Ear Cleaner has been subsequently tested using the same protocol. The surprise results were that only the alcoholic ear cleaning products (Leo Ear Cleaner, the compounded product, Milo's ear cleaner) and neat propylene glycol showed any significant activity (>80% mean percentage of synthetic cerumen removed) and all other products showed a wax-removing activity equivalent or less than that of water alone. Interestingly, the lower concentration of propylene glycol found in Ilium Otoclean did not seem to be an effective ceruminolytic.

While this study had a rigid protocol, and was not without its limitations, the results corroborate most of the author's clinical experience. One of the study limitations was that no follow-up flushing was allowed as part of the protocol. In the author's clinical experience, PAW Gentle Ear Cleaner is an effective surfactant ceruminolytic (in contrast with the study), but only where thorough flushing is feasible afterwards. The alcoholic ceruminolytics also seem to perform better with flushing (the author not uncommonly uses Epi-Otic for this in the home setting), and that is the manufacturer recommendation for Bayer Clean Ear Solution.

The take home message is that if the right cleaner is used in an ear with predominantly ceruminous exudate, it should be able to be effectively clean the ear canal, probably within a week, if done correctly. If it is not improved in this time, then GA and flush should be reconsidered.

There are no comparative studies investigating the performance of ear cleaners in their efficacy at removing purulent or primarily keratinous exudate so the only means of judging this is clinical experience and an understanding of the active ingredients.

It has been reported that most ceruminolytics are of questionable benefit in ears with a purulent discharge. Surfactant ceruminolytics such as the PAWS Gentle Ear Cleaner should, however, be effective with purulent exudates, but as previously mentioned, will perform best when followed by flushing. Alcoholic solutions, while antiseptic and potentially causing proteins to precipitate (thereby facilitating removal), will almost invariably sting where there is erosion or ulceration of the ear canal, as is commonly seen with purulent exudate. This makes them of limited value in these cases. Acetic acid and lactic acid may also precipitate proteins in ears with purulent exudates facilitating their removal, though the former can also cause irritation.

Ears with macerated keratinocytes are likely to benefit from use of alcoholic ear cleaners such as the Milo's Ear Cleanser because of their drying action. Ears with predominantly dry keratinous exudate (e.g. sebaceous adenitis, pemphigus foliaceous) may benefit from the keratoplastic effects of salicylic acid in Epi-Otic or phytosphingosine in Douxo Micellular Solution (not readily available in Australia but used by the author) or the humectant effect of propylene glycol in Ilium Oticlean.

Antimicrobial Effects

Several studies have examined the antimicrobial effects of some of the ear cleaners available in Australia both *in vitro* and *in vivo*. Basset *et al* (2004) showed Malacetic Otic to have good efficacy against cases of *Malassezia* otitis. Good compliance was essential to good results in this study. Epi-Otic, when used against first line mixed (*Pseudomonas*, *Malassezia* or *Staphylococcus*) infections (not chronic), showed 68% of ears infection free after 2 weeks (Cole, 2005). *In vitro* Epi-Otic showed rapid activity (< 1minute) against these three organisms also though another study showed the kill time of *Malassezia* to be somewhat slower (Lloyd et al, 2002). Tris EDTA shows significant activity alone against *Pseudomonas* especially and other Gram negative rods to a lesser extent, and, if not outright bactericidal, can damage the bacterial cell wall to reduce bacterial antibiotic resistance (Cole, 2005), especially to aminoglycosides and fluoroquinolones. Gbadamosi & Gotthelf (2003) showed *in vitro* that 12 enrofloxacin and ciprofloxacin resistant strains of *Pseudomonas aeruginosa* became susceptible to enrofloxacin following 5 minutes incubation with Triz EDTA. In contrast, using a different *in vitro* model Swinney et al (2008) found Triz EDTA to have no antimicrobial activity, but Triz Plus, Malacetic, an ear cleaner with listed ingredients the same as Epi-Otic and an ear cleaner with listed ingredients similar to Milo's Ear Cleanser to have antimicrobial efficacy against *Pseudomonas aeruginosa*, *Staphylococcus* (*pseud)intermedius* and *Malassezia pachydermatis*.

pH of Ear Cleaners

The pH of skin tends to rise with inflammation. In humans, treatment of mild otitis with acidifying ear cleaners is often successful, and normalising of pH is associated with clinical cure. The pH of normal canine and feline skin is 5.5-7.5 depending on the species (higher in dogs), day, body site (lower on the pinnae), breed, and sex. It has been reported to increase with inflammation. In cats and dogs, there are three possible effects pH may have in otitis.

Firstly, the pH of the otic environment can affect antibiotic activity and stability. Some antibiotics work better in slightly alkaline environment (fluoroquinolones, aminoglycosides), and some show less efficacy in an acidic environment (fluoroquinolone slightly and aminoglycosides markedly). Timentin may degrade in a low pH. Chloramphenicol is active at a wide range of pH.

Secondly, microbial growth may be affected by pH. While staphylococcal species and *Malassezia pachydermatis* can grow at a wide range of pH, acidity of less than 5.5 and 4 respectively can decrease microbial growth *in vitro*.

Thirdly, an acid pH may, theoretically, help regulate keratinisation in a previously inflamed ear. In practice this effect remains unproven.

Other Effects

Timentin solution can degrade at an accelerated rate if exposed to metal ions. Tris EDTA binds metal ions and this may help prevent degradation of Timentin in the ear.

Acetic acid (2.0–5.0%) has been reported as an effective astringent (drying agent) but the author has found the alcoholic nature of Milo’s Ear Cleanser most effective of the available ear cleaners in Australia for this purpose.

Administration: How to Use?

When it comes to clients cleaning problem ears, the author works on the premise that if the ear is to be cleaned and the entire canal treated, it needs to be kept as doable as possible (to improve compliance – this usually means once daily) and the product used generously enough to effectively bath the ear canals (to maximise efficacy and treatment of the entire canal). This approach comes with a few limitations, these being that:

- the client must be able to perform the administration correctly
- it probably increases the risk of irritation from some of the products
- it increases the risk of maceration with prolonged use (or drying with respect to alcoholic ear cleaners)
- some products may not work as effectively e.g. Bayer Clean Ear Solution where the manufacturer recommendation is syringing of the ear with warm water after application, but this is infrequently achievable by clients at home. Also, when Epi-Otic is used as a sole therapy, it has its best antimicrobial performance when used twice daily.

The instructions then generally given to clients are (and demonstration of this is extremely important – do not assume they can do it correctly unless they have done it correctly before!):

- Go somewhere where it does not matter if ear clear is spilled (outdoors, laundry etc).
- Hold the ear at right angles to the head to open up the canal (the muzzle and ear should form a horizontal right angle parallel with the floor).
- Fill the ear until product starts to spill out. A 3-5ml syringe may be useful for this. Try to warm the ear cleaner a little if possible.
- Place a cotton ball in the entrance of the ear canal.
- Massage the cartilaginous part of the canal between the opening of the canal and where it joins the skull until a squishing sound is achieved. If this sound is not achieved then there is likely not enough fluid in the ear or the massaging technique is incorrect. This is essential for mechanically assisting distribution of the ear cleaner in the canal. It is also why ear cleaners sometimes struggle to remove material from the osseous part of the ear canal (i.e. the part that runs through the skull).
- Continue for about 1-2 minutes. Replace the cotton ball if it becomes soaked. This is a long time and often I will say to clients continue till your hand gets a bit sore. Top up with ear cleaner in this time if it is running low if necessary.
- Once this is complete allow the dog to shake out as much as possible.
- Wipe out excess cleaner with a cotton ball from the pinna and external canal.

The frequency and timing of administration with respect to ear ointments, and duration of therapy vary with the case and product.

Problems to Watch For

There are three major complications to watch for with ear cleaner use:

Irritation

While a short period of irritation post ear cleaning is not unexpected, it should not persist more than a minute or two.

Longer than this and use of the ear cleaner should be reconsidered, especially if seen in association with an inflamed medial pinna, which can be extreme. Ear cleaners with a higher potential for irritation include those containing acetic acid, with a very low pH or containing significant amounts of alcohol, especially in the face of pre-existing inflammation. Topical drug eruptions may also occur occasionally to components of ear cleaners. Note that reactions can also be seen secondary to ear ointments and sometimes this will need to be differentiated from a reaction to the ear cleaner.

Maceration

This is common following prolonged use of non-alcoholic ear cleaners, especially when used twice daily. It is identified by a generally creamy pale exudate, and on cytology only keratinocytes and neutrophils can be seen, often (though not always) in the absence of any micro-organisms. Cessation of use of the ear cleaner along with sometimes oral glucocorticoids is required though secondary infection needs to be closely monitored for as the wet ear canal normalises. Alcoholic ear cleaners can speed this process of drying.

Ototoxicity

Virtually all commercially available ear cleaners in Australia are potentially ototoxic, with the exception of Triz EDTA (and Triz Plus, though this is not commercially available). Because of this, all clients should be warned that ototoxicity is a risk where the ear drum cannot be observed to be intact. This ironically, is most of the cases that require cleaners. Clinical signs to watch for are loss of balance, circling, loss of hearing (though other factors may cause this such as ear ointments reducing conductive hearing), nystagmus, and/or facial droop. If any of these are reported, then the dog should be rechecked ASAP and, if necessary, an ear flush performed. Most cases of ototoxicity are reversible at least partly if the bulla is aggressively flushed within a short space of time.

Acetic acid in a 2-2.5% aqueous solution (equivalent to a 1:1 to 1:3 dilution of white vinegar with saline or distilled water) has been recommended by several reports as being safe in the presence of ruptured TMs. The author has used aqueous 2% acetic acid / 2% boric acid (~ pH 5.8) with no observed ototoxic effects in similar cases. However, acetic acid has been reported as damaging to the cochlear hair cells in chinchillas, guinea pigs and rats and is dependent on pH, and duration of contact, with acetic acid at pH 4 causing total deafness by 24 hours, and acetic acid at pH 5 causing partial hearing loss after one week. Definitive studies in companion animals are needed.

Follow Up

The efficacy of ear cleaners should always be reassessed after 1-2 weeks. If the ear exudate is not clearing and cytology is not significantly improved in this time then treatment (both cleaner and ear ointment if used) should be reassessed, and most importantly so should client compliance! Asking a client to demonstrate their ear cleaning technique in the consult room will sometimes reveal the source of therapeutic failure.

PHYSICAL EAR CLEANING: EAR FLUSHING UNDER ANAESTHESIA

Only rarely does the author get a patient on the table for an ear flush and wonder why he bothered. On the other hand, he is far more often surprised by the amount of exudate present and is relieved to be doing the flush! The key to successful ear flushes are patience (allow up to an hour per ear for very severe cases), visualisation (hand held otoscope vs video otoscope), the right cleaning tools and practice, practice, practice. Even with the best equipment cleaning an ear can be an exercise in frustration without acquiring the skills to do it right. At the authors practice, the role of the nurse is key in cleaning an ear, from setup, to keeping things running smoothly with the anaesthesia and actually performing a lot of the flushing and cleaning under the vets direction through to recovery.

Another important prerequisite to a successful ear examination and flush is having a canal to work with. Attempting to examine and flush a severely stenotic canal is unlikely to be successful. Where a canal is stenotic because of inflammation or epidermal hyperplasia, attempts should be made to open the canal up prior to flushing. See the previous lecture for details.

Hand Held Otoscopy vs Video Otoscopy

The majority of practices have access to hand held otoscopes, but video otoscopes are still relatively uncommon in this country. Both have advantages and disadvantages but because of the better visualisation of deep canal structures, the author uses a video otoscope.

Hand Held Otoscopy

Advantages include a bigger working channel, lower cost, possibly better visualisation than video otoscopy if the canal is dry and is of a large diameter. Disadvantages are the need to constantly remove fluid to assess progress, reduced magnification compared with video otoscopy, and the difficulty in seeing the deeper structures of some ears, especially if the canal is stenotic.

Video Otoscopy

Advantages include better visualisation (esp. with water in the canal), that all operators can see the canal, and recording of the procedure is possible for both records and clients. Disadvantages include higher cost, a smaller working channel (2mm), longer setup, and the larger equipment storage space required.

Setup

No matter if hand held or video otoscopy is used, the setup for both is nearly the same because the cleaning technique is similar for both. Prior to the patient being on the table, there should be ready to go:

- ± video otoscope
- a hand held otoscope (with several cones if handheld)
- (preferably cordless) clippers for trimming medial pinnal hair
- dry swabs for pinnal and otoscope cleaning
- a dish of alcohol-soaked swabs for cleaning the biopsy forceps, curette and video otoscope
- a hand towel (to cover the patient’s eyes)
- a rolled towel to support the patient’s neck
- a covered heating pad & blanket to cover the patient if a long flush is expected
- a 5 Fr feeding tube (larger OK if hand held otoscope) with the fenestrated tip cut off for flushing (one per ear)
- several 12ml syringes

- a kidney dish for holding warm saline
- at least 2 x 1L bottles of sterile saline for flush, one hot, one cold
- microscope slides and pencil for labelling
- disposable gloves (for both operators; facemasks and eye protection are also ideal to minimise contamination from infected aerosols)
- cotton buds
- Epi-Otic (or equivalent solution for pinnal cleaning)
- PAW Ear Cleaner (if required for residual exudate cleaning)
- haemostats (for hair plucking if required)
- cup-type endoscopic biopsy forceps
- otic curettes

The last two pieces of equipment are key to being able to remove the variety of exudate found down the ear. Regular cup-type endoscopic biopsy forceps are easily and relatively cheaply available but the length of them can make handling awkward. Much shorter forceps are available through at least two companies but ironically are significantly more expensive, so if you have them treat them well!

http://www.karlstorz.com.au

http://www.medrx-usa.com/WebSite/pages/VET/BiopsyTools.html

The otic curettes come in two sizes. For hand held otoscope the author would only recommend the larger size, but for video otoscopy both can be useful – the larger one is inserted into the scope retrograde but the smaller on can fit normograde down the working channel. These are less expensive than the short biopsy forceps.

Getting the Patient Ready

In severely affected ears, use of opioids as part of the premedication may help with subsequent pain management. An alternative is to use local anaesthesia to achieve this. Auriculotemporal and great auricular nerves provide sensory innervation to the external ear. These nerves may be blocked with 1-2 ml of 2% lignocaine or prilocaine, or 0.5% bupivacaine. Block the auriculotemporal nerve by injecting local anaesthetic solution rostral to the vertical ear canal and caudal to the temporal component of the zygomatic arch. Block the great auricular nerve by injecting local anaesthetic solution caudal to the vertical ear canal and ventral to the wing of the atlas.

Once the dog is stable with the anaesthesia, a towel should be rolled up and placed under the neck so the nose tilts downwards from the ears. In this way if the ear drum is ruptured then the flush fluid will run out of the nose and not back down the pharynx. Well cuffed endotracheal tubes will also minimise the risk of aspiration if any fluid does drain down the trachea.

Excess hair should then be clipped from the medial aspect of the pinna and excess exudate removed from the pinna and around the entrance to the ear canal using dry swabs and cotton buds. Be a little gentle as cotton is quite abrasive to inflamed skin. A few Epi-Otic soaked swabs can then be used if required for removal of any remaining attached wax or scale. Do not let any solution run down the canal at this stage. Once this is done, if the canal is excessively hairy then the hair should be removed using haemostats. One of the bottles of saline should be heated in the microwave (loosen the lid first) to about 40-50ºC and then a kidney dish half-filled with a mixture of this and the cold saline to make it body temperature. This saline will be used for flushing. By using the one hot and one cold saline it saves multiple trips to the microwave during the procedure as the saline cools. Lastly, the handtowel can be placed over the eyes to protect them from spilling flush fluid. At this point, the flush of the ear can start proper.

The Examination and Flush

Following initial examination of the canal, it is useful to get a sample of the exudate from the vertical canal for cytology if this has not already been taken. Cytology from the vertical canal is not always the same as cytology from the horizontal canal, especially in chronic cases so it pays to get samples from both locations. Vertical canal samples can be taken with a cotton bud and rolled out on a slide and labelled. Samples should be collected from the horizontal canal from all affected ears for cytology as soon as possible after the commencement of the flush – by the time the flush is completed it may be too late to sample the canal! Samples (often collected by suction or with the forceps) can be placed on a slide, made into a squash preparation and labelled for examination after the procedure has finished.

When it comes to removing exudate there are really only three mechanical ways to do it – flushing with warmed fluids, grabbing with biopsy forceps or scraping with an otic curette. All three are variously useful with different types of exudate.

Flushing is typically done with a 12ml syringe attached to a 5fr (or larger if feasible) feeding tube. Body temperature saline is made in a kidney dish using saline from the ‘hot’ and ‘cold’ bottles. Saline that is too cold may be uncomfortable and potentially ototoxic if the ear drum is ruptured, and may cause burns if too hot. If over the course of the flush, the saline temperature drops and is too cool, then some saline from the ‘hot’ bottle can be used to warm up the flush fluid, or the current batch of saline can be dispensed with and a fresh batch made up from the ‘hot’ and ‘cool’ saline bottles. The pressure generated with a 12ml syringe and 5fr feeding tube should not be sufficient to rupture an ear drum in 99% of cases unless it is already very inflamed and damaged, in which case the clinician may need to be a little more gentle to avoid perforation.

Technique-wise, it is often better to insert the feeding tube to a deeper part of the canal and backflush material up the ear rather than try to blast it from above. A pulsing action can help dislodge some pieces of trapped exudate more effectively. Again, it is difficult to manually rupture an intact ear drum with a 5fr feeding tube (though not impossible) as it is too soft. Flushing may be done repetitively with the excess fluid and exudate coming out the top of the ear canal, or alternatively by cycling between flushing and aspiration. The latter is a little slower but preferable for hand held otoscopy where a fluid-free canal is essential for visualisation. Flushing is the only one of the three basic cleaning techniques safe for cleaning middle ears where the TM is already ruptured by the time of the flush.

The nose should be closely observed while flushing. If copious fluid is running out the nose concurrently with the flush then the ear drum in that ear is ruptured and this will need to be taken into account with subsequent medications. If there is any doubt about this, then a very small amount of iodine solution (not scrub which is ototoxic) should be placed in the saline till it is just a light brown (concentrations <1:4 were not ototoxic in chinchillas). Flushing is then done with this and a dry clean swab used to dab the nose to assess the colour of fluid coming out – if tinged brown then this confirms ear drum rupture. Note that while this is a specific test, it is not perfectly sensitive as some dogs with ruptured TMs will not have fluid running from the nose with flushing.

Larger, more solid pieces of exudate and deep hair are often removed more quickly with biopsy forceps. The person operating the otoscope should give directions to the person flushing / grabbing ('up', 'down', 'open', 'close', ‘in’, ‘out’ etc) to enable grasping of the exudate. Because movement of the end of the flush tube / forceps is a result of both operators, a continuous exchange of information is required to ensure the tip gets to where it needs to go without causing any damage to the otic structures. This is easier with a video otoscope where both parties can see the ear canal on the screen. The best way to maintain fine control over the biopsy forceps is to have the hand holding the forceps resting on the otoscope so as to maintain movement of the forceps with the otoscope itself. To best control opening and closing have the other end of the forceps in the palm of the hand and move the opening / closing slider with the thumb and forefinger. Good control of the biopsy forceps is essential to avoid iatrogenic perforation of the ear drum.

Ceruminoliths if present are often able to be removed completely with biopsy forceps. Their texture and composition varies however, and some end up being debulked with biopsy forceps before being flushed out. Occasionally a ceruminolith is stuck to the TM, and damage to the TM in these cases may be unavoidable if the ceruminolith cannot be broken up using chemical means. It should be noted that aggregation of debris in the osseous part of the canal over time can create a sacculation in the par tensa, pushing it back into the bulla and potentially giving the impression of a ruptured middle ear. This ‘false’ middle ear typically bounces back quickly within a few days and may appear to be a rapid regrowth of what was thought to be a ruptured TM.

Lastly, the otic curette can be used to scrape out material. More often than not this is simply held in place by the operator of the otoscope, and then the otoscope itself moved to facilitate cleaning. Alcohol-soaked swabs should be used throughout the procedure for routine cleaning of the otoscopic cone / handpiece, biopsy forceps and otic curette.

Other reported cleaning techniques include:

- Use of a warmed saline bag and giving set with a 3 way tap attached to a feeding tube which is then inserted into the otoscope. A 10ml syringe is attached to the 3 way tap and use of the tap then allows repetitive and rapid flushing and refilling of the syringe. (M. Burrows, personal communication, 2009)
- Use of a suction unit attached to a second feeding tube concurrently with the flushing feeding tube. This is not possible with the narrow working channel of a video otoscope but may be desirable with hand held otoscopy.

- Use of an Earigator (MedRx) pump. This allows alternate flushing and suction through the one feeding tube using a trumpet like device. Setup and cleaning of this device nullifies some of the time advantage gained by faster flushing.
- Calcium glycolate has been studied in normal dogs as a chemical depilatory and shown not to induce side effects such as erythema, pain, or inflammation. Studies were conducted in anaesthetised patients.
- Use of 1:1 to 1:3 white vinegar (acetic acid) instead of saline for flushing in ears with *Pseudomonas* otitis. One minute contact with 2% acetic acid kills *Pseudomonas*.
- Use of PAWS cleaner or Waxsol (if very waxy ears) to soften the exudate first (fill ears, massage well for a few minutes and leave to soak for 2-10 minutes) and then saline is used to flush afterwards. Initial post-soak flushing may be done with a bulb syringe to remove larger fragments of debris. Make sure there is space in the canal around the bulb syringe to allow for flush fluid to escape to minimise the risk of iatrogenic TM perforations. If the TM is already ruptured, repeated extensive flushing of the middle ear should be performed to remove the ear cleanser, as many ceruminolytic agents are ototoxic (Nuttall & Cole, 2004; M. Shipstone, personal communication).
- Alligator forceps are also useful, especially for cornified plugs, hairs and foreign bodies, but it may be difficult to open the jaws sufficiently in narrow ears.

Following the main part of the flush, if the ear drum can be completely seen to be intact and no fluid is seen to come out the nose then the author will often fill the ear canal with PAWS ear cleaner, massage then flush repetitively until the bubbles are no longer present. This is very useful for removing residual exudate (especially ceruminous) in many cases. PAWS ear cleaner has a very surfactant (detergent-like) action and while it is a good cleaner on the table it is important to flush well afterwards with saline. **If there is any doubt about the state of the ear drum then do not use it as ototoxicity has been anecdotally reported on at least two occasions where the ear drum was not intact, even with aggressive flushing afterwards.**

The temperature of the patient should be monitored periodically during the flush, especially during longer procedures. Additional warmth should be applied if required.

Once the ear canal is clearly visible, notes should be recorded as to any abnormalities including the integrity of the TM, the state of the lining of the ear canal (glandular and epidermal hyperplasia, stenosis due to oedema versus stenosis due to fibrosis), and any tumours (neoplastic or inflammatory). These records can be used as a baseline for improvement subsequent to follow-up therapy.

Tumours: To Biopsy or Not?

Common tumours of the ear include inflammatory polyps (most common), ceruminous adenomas, ceruminous adenocarcinomas, plasmacytomas and squamous cell carcinomas though any tumour potentially affecting the skin may also affect the ear canal. If a tumour is found in the ear canal then removal at flushing may be curative, or at least will allow a prognosis to be given to the client. Fortunately the ear cartilage tends to limit spread of tumours, but tumours arising from the middle ear can on occasion invade bone and this will lead to a worsening of the prognosis. Biopsies of tumours are usually achieved with biopsy forceps through the otoscope, though some fine electrocautery loops may be appropriate for removal of tumours.

Generally speaking, most tumours that are not polyps will need surgical intervention of some sort to cure, and recurrent otitis if this is not done is often the sequelae. The location of the tumour will dictate the best surgical option – this will be discussed in a subsequent lecture.

Inflammatory polyps can arise from the ear canal wall, or grow out from the middle ear and rarely from the nasopharynx! The cause of them is unknown but a response to infection may be involved. They are typically pedunculated, which allows for easier removal in many cases, but their fibrous nature makes them occasionally difficult to grab. Where a polyp can be grasped, it is best to remove the polyp with gentle traction to try and remove the stalk of the polyp also. Gentle traction can help disrupt the vascular supply to the residual stalk, minimising the chance for regrowth rather than cutting which leaves the blood supply intact. Following removal, anti-inflammatory therapy is required to further minimise the chance of regrowth. This should be done via oral medications and some topical corticosteroid solution delivered (e.g. Depomedrol) to the residual base of the polyp. Despite therapy, about a third of polyps will regrow. The author uses this technique with polyps arising from the external canal only. Because of the probability of failure of TM regrowth and because of damage already done to hearing and auditory ossicles, polyps arising from the middle ear may be better treated with a total ear canal ablation. Other reports suggest these may also be removed by traction or bulla osteotomy, but the author remains guarded about the long term prognosis for these cases because of the anatomical issues above.

Myringotomies

Where there is evidence for otitis media (radiographic, advanced imaging, neurological, directly observed TM changes), then myringotomy may be indicated. The aim of myringotomy is to sample the middle ear for culturing and cytology, flush out any abnormal material that is possible to remove and not cause further problems. Infection in the middle ear may not be the same as infection in the external ear and this needs to be identified where relevant. Myringotomy should be performed following cleaning and antiseptic treatment of the external ear canal because the possibility of spreading infection from the external ear to the middle ear, or contaminating middle ear samples needs to be minimised. Following cleaning of the external canal, the canal should be flushed with a 0.1% chlorhexidine or dilute iodine solution, then rinsed with sterile saline and fluid removed. A 5fr tomcat catheter, sterilised with chlorhexidine and rinsed with sterile saline and with the tip cut to a 60 degree angle, is then passed through the otoscope to perforate the TM. The dorsal rostral area of the TM should be avoided to minimise damage to the auditory ossicles. 0.5-1ml of sterile saline is infused and aspirated from the middle ear for collection. Subsequent to that, a soft sterile 5fr feeding tube can be passed through the hole and the middle ear repetitively flushed and aspirated with warm sterile saline until clear. Under normal circumstances the TM should heal in 2-4 weeks but clients need to be warned that there is a risk of non-healing occasionally in some patients. Note that medications not safe for use in the middle ear should not be subsequently used in that ear until the TM is healed. This can present therapeutic challenges. Reassessment of the TM may (or may not) require subsequent sedation for close observation.

Other reported myringotomy techniques include:

- with hand held otoscopy, directly passing a sterile mini-tipped culture swab through the TM to the bulla
- use of a sterile Steinmann pin to initially perforate the TM

Immediately Post Procedure

Once the ear flushing has been completed, then the pinna should be cleaned again to remove any flush and exudate. Where the TM is intact, use of a drying agent such as Milo's Ear Cleanser is useful to help excess flush material evaporate. This is important because a wet ear post flush is more predisposed to infections (especially yeast).

Otic cones should be changed between ears / patients, as well as using new flush fluid, feeding tubes, and syringes to prevent cross infection between ears. Otic curettes and biopsy forceps should be cleaned thoroughly with chlorhexidine and alcohol or better yet autoclaved. Swabs should be topped up and flush fluid reheated if necessary.

Flushing of ears, especially inflamed ears, can be painful, and post procedural pain relief is important for the patient (if it has not already been administered prior to the procedure). It will maximise subsequent topical therapy compliance – pets experiencing pain make it difficult to administer medications. Extremely inflamed ears may also benefit from an IV injection of 0.1mg/kg dexamethasone NaP if the patient is not already on glucocorticoids.

Finally, cytological samples should be stained with Diff Quik or equivalent for examination and subsequent determination of appropriate medications.

Complications

Ear flushing, while low risk, is not a risk-free procedure. Aside from anaesthetic risks, cases have been anecdotally reported with vestibular signs or deafness post flushing, even when no ototoxic medications have been used. These side effects are rare and usually transient when they occur. One study of 105 dogs showed no loss of hearing as measured by brainstem auditory evokes response testing, and measurable improvements in several dogs. Nonetheless, damage leading to vestibular syndrome, facial nerve paralysis, Horner's syndrome or deafness is a potential concern when ear cleaning, particularly when using more aggressive techniques including myringotomy. The risk may be higher in cats.

Failure of ear drum healing is also a rare risk where myringotomy has been performed, or if the TM has been chronically ruptured, and now has a non-healing perforation, or if the germinal cells of the TM have been ablated and there is simply no more TM left to grow back.

Clients also need to be aware that chronic changes in the deep aspect of the canal may lead to failure of the cleaning procedure. Good communication before the flush, emphasising that the point of the exercise is as much about information gathering in the deep canal as it is about cleaning, should minimise false expectations. Ultimately, it is prudent to obtain informed consent prior to ear flushing outlining potential risks in writing.

Follow Up Over the 1-2 Weeks Following Successful Flushing

While a clean ear is halfway to being cured, it can quickly relapse if undertreated after cleaning. It is important to remember that it will almost certainly still have some residual infection, and that this will quickly recolonise the inevitably abnormal canal because the canal still has a microenvironment favourable for microbial growth. As has been previously outlined, the goal at this point is to control pain, inflammation and infection, and to normalise the lining of the ear canal as best as is possible. It is entirely possible for the ear to rapidly relapse if subsequent therapies are not correctly instituted.

Inflammation

If use of topical glucocorticoids is insufficient for inflammation control, then prednisolone 0.5-1mg/kg q24h tapering over 2-4 weeks should be used. NSAIDS do not seem as effective in this capacity.

Pain Control

If oral glucocorticoids are not being used then NSAIDs may be appropriate for pain relief. If glucocorticoids are being used systemically then tramadol 1-4mg/kg PO bid for 5-7 days is appropriate. Sedation, dizziness and anxiety have been reported as possible side effects though the author has found these to be rare.

Infection Control

Topical antimicrobials (and occasionally systemic antimicrobials) should be instituted depending on organisms identified on cytology, the state of the TM and occasionally, *in vitro* sensitivities. This will be dealt with in a separate lecture.

Ear Canal Normalisation

In chronic cases of otitis, even with underlying causes addressed successfully, it can take many weeks to months before the ear canal is near normal. Topical therapies, while essential to resolution of most cases still create an abnormal ear environment and ultimately must be tapered off. However, this should be done slowly in chronic cases, so as to continue to provide cover for infection while allowing the ear canal to normalise and dry. Concurrent anti-inflammatory medication should be continued through this process and tapered concurrently. Once the ear canal is grossly near normal on otoscopy and infection and inflammation controlled, the author typically weans the topical medications to q48 hours for 3 doses then q72h for 2 doses prior to cessation, and then rechecks the patient after 14 days. Relapse will occasionally occur in this period and the client should be warned of this possibility. Rechecks are essential until the patient is off medication (or onto maintenance level medications) and stable.

Note that this tapering protocol is not necessary in acute cases where significant ear canal changes have not occurred.

Exudate Control

The author rarely uses ear cleaners in the period immediately following an ear flush as the ear is already clean, and if inflammation and infection are controlled, the immediate reaccumulation of exudate in the following weeks should be preventable in most cases. Very chronically affected ears may still produce significant amounts of exudate despite the best attempts to slow it down, and a second flush may be periodically required. A prominent exception is the use of tris EDTA to assist in clearing Gram-negative rod infections (primarily *Pseudomonas*).

Long Term Follow Up

For a single episode of otitis (and a single episode may be months or years in duration), or where no evidence for relapse of disease can be provided, where no persistent cause for otitis is identified, and the ear canal is normal at resolution, then no maintenance is required aside from regular rechecks for possible relapse.

On the other hand, the maintenance of ears prone to relapsing ear disease is problematic and there is no simple solution. The right maintenance approach depends entirely on the underlying triggers of microclimate change in that particular ear. As has previously been mentioned, the clinician needs to look at the WHY of the otitis to best select approach to therapy. Ideally the best approach is to deal with the underlying cause if possible (allergies, swimming, etc). However, if the underlying problem cannot be identified or treated, then the nature of the recurrent infections can dictate the most appropriate ongoing ear cleaner. Table 13.2 summarises which ear cleaners are likely to be useful in different situations for maintenance. Some cases require 1-2 times weekly otic ointments to best control inflammation and infection, but doing this increases the possible risk of development of antimicrobial resistance, and ideally should not be used long term. In any case, periodic (3-6 monthly) rechecks are recommended to ensure maintenance therapy is achieving its goals.

It is important to realise though, that for some underlying diseases (e.g. recurrent foreign bodies, topical irritants such as shampoos, ear parasites, large polyps, severe stenosis) routine ear cleaners are not indicated and where used are unlikely to prevent recurrence of problems.

ONE LAST ISSUE: TO PLUCK OR NOT TO PLUCK?

In the vast majority of cases, plucking as a preventative therapy for otitis is not recommended, and can in fact be counter productive in some dogs prone to relapsing otitis. Plucking of hair leads to a traumatic folliculitis which can trigger otic inflammation and create the conditions ripe for infection again. This is seen when dogs get otitis in the week after grooming and having their ears plucked.

Hair alone for a majority of dogs is NOT enough to lead to relapsing otitis – if this were the case then every Poodle or Bichon Frise would be getting infected ears regularly and this is clearly not the case. On the other hand hair can slow drying of ears leading to maceration, and in these cases it is the maceration that triggers the infection not the hair.

Having said that, where dogs with hairy ears already have otitis with significant exudate and matting of ear hair, ear plucking is mandatory to facilitate penetration of topical medications. This again is best done under GA at the time of ear flushing so hairs right down the canal can be removed if required.

Table 13.2. Ear Cleaning Products

Product Name	**Declared Composition**	**Manufacturer**	**Comments & Usage Guidelines**
Bayer Clean Ear Solution	Enzymes (esterases, lipases, phosphohydrolases) from fermented plant and molasses extracts (20%), water (>60%)	Bayer Animal Health Australia	• Maximum ceruminolytic performance when followed by flushing • Would not expect to be effective for purulent or keratinous exudates • No known antimicrobial activity • Non-irritant • Would expect maceration with prolonged frequent usage • Useful vehicle to make up to 0.5% dexamethasone NaP to use 1-2 times weekly for prevention of allergic otic inflammation
Compounded product	2% acetic acid, 2% boric acid in an aqueous solution	Compounded product	• Mild astringent • Lack of reports of ototoxicity in the dog – may be middle ear safe • Efficacious for *Malassezia*, *Pseudomonas* but NOT *Staphylococcus* (despite *in vitro* evidence to the contrary) • For *Malassezia* use once daily for 7-14 days then twice weekly till recheck • Contact time (ideally > 2min) in ear important for efficacy • pH ~5.8; may help normalise otic keratinisation long term • Little ceruminolytic activity or ability to remove keratinocytes though may be more efficacious with removal of purulent exudate • May cause irritation in some patients • Would expect maceration with prolonged frequent usage • Can be used 1-2 times weekly for maintenance to try and decrease the frequency of recurrent yeast infections but on its own was not found to be effective in one study for this • Useful vehicle to make up to 0.5% dexamethasone NaP to use 1-2 times weekly for prevention of allergic otic inflammation with recurrent yeast infection
Duoxo Micellular Solution	Phytosphingosine (0.2%), Nonionic surface-active agent, polidocanol, polysaccharides, fragrance	Sogeval US *	• Minimally ceruminolytic or effective for removal of keratinous exudate • Phytosphingosine has keratoplastic effect in normalising excess scaling – good for use in sebaceous adenitis or in the post flush period of normalisation • No known antimicrobial activity though other salts of phytosphingosine have demonstrated antibacterial activity • Possibly ototoxic based on ingredients, and not recommended with perforated TMs • Non-irritant • Would expect maceration with prolonged frequent usage but this should not be an issue with recommended usage of 1-2 times weekly

Table 13.2. Ear Cleaning Products (cont'd)

Product Name	Declared Composition	Manufacturer	Comments & Usage Guidelines
Epi-Otic	Salicylic acid (0.11%), lactic acid (2.5%) docusate sodium, propylene glycol and chloroxylenol	Virbac (Australia) Pty Ltd	• Minimally ceruminolytic • Acids may be useful in removal of proteinaceous exudates • Keratoplastic effects of salicylic acid and acidity (pH ~2.5) potentially useful for normalising scaling • Minimally irritant • Weak astringent • Probably ototoxic based on ingredients, and not recommended with perforated TMs • Moderate antimicrobial activity with twice daily use (reasonable over the counter choice for otitis sight-unseen but maceration probable with prolonged use at this or daily frequency) • May be used 1-2 times weekly for maintenance to try and decrease the frequency of recurrent mixed infections • Useful vehicle to make up to 0.5% dexamethasone NaP to use 1-2 times weekly for prevention of allergic otic inflammation with recurrent mixed infections • Can be used as a flush after more effective ceruminolytic cleaners at home
Ilium Oticlean Skin and Ear Cleansing Solution	Malic Acid (2.25%), benzoic acid (0.15%), phenol 0.037%, propylene glycol (40%)	Troy Laboratories	• Mild astringent • Minimally ceruminolytic • Propylene glycol may be a good choice for dry ears, useful for purulent exudate? • Unknown anti-microbial activity though likely some because of organic acids and propylene glycol
Malacetic AP Ear / Skin Cleaner for Pet	Acetic acid (2%), boric acid (2%), fragrance, water	Dermapet Inc (Distributed in Australia by Ceva Delvet Pty Ltd, Australia)	• Mild astringent • Lacks propylene glycol of regular Malacetic Otic – may be middle ear safe but not recommended if TM perforated • Efficacious for *Malassezia*, *Pseudomonas* but NOT *Staphylococcus* (despite *in vitro* evidence to the contrary) • For *Malassezia* use once daily for 7-14 days then twice weekly till recheck • Contact time (ideally > 2min) in ear important for efficacy • pH ~5.8; may help normalise otic keratinisation long term • Little ceruminolytic activity or ability to remove keratinocytes though may be more efficacious with removal of purulent exudate • May cause irritation in some patients • Can be used 1-2 times weekly for maintenance to try and decrease the frequency of recurrent yeast infections but on its own was not found to be effective in one study for this • Useful vehicle to make up to 0.5% dexamethasone NaP to use 1-2 times weekly for prevention of allergic otic inflammation with recurrent yeast infection

Malacetic Ear / Skin Cleaner for Pets	Acetic acid (2%), boric acid (2%), propylene glycol (5%), fragrance, water, surfactants	Dermapet Inc (Distributed in Australia by Ceva Delvet Pty Ltd, Australia)	• Mild astringent • Not recommended if TM perforated • Efficacious for *Malassezia*, *Pseudomonas* but NOT *Staphylococcus* (despite *in vitro* evidence to the contrary) • For *Malassezia* use once daily for 7-14 days then twice weekly till recheck • Contact time (ideally > 2min) in ear important for efficacy • pH ~5.8; may help normalise otic keratinisation long term • Little ceruminolytic activity or ability to remove keratinocytes though may be more efficacious with removal of purulent exudate • May cause irritation in some patients • Can be used 1-2 times weekly for maintenance to try and decrease the frequency of recurrent yeast infections but on its own was not found to be effective in one study for this • Useful vehicle to make up to 0.5% dexamethasone NaP to use 1-2 times weekly for prevention of allergic otic inflammation with recurrent yeast infection
Milo's Ear Cleanser	Menthol (0.91%), chlorothymol (0.1%), boric acid (2.37%), isopropyl alcohol	Ceva Delvet Pty Ltd, Australia	• Effective drying agent, but overuse can lead to overly dry, irritated ears • Not recommended if TM perforated • Ingredients efficacious for *Malassezia*, *Pseudomonas*, *Staphylococcus in vitro* but lacking *in vivo* studies • Excellent ceruminolytic activity but some cases may do better with flushing afterwards with another cleaner e.g. Epi-Otic • Use once daily up to 2 weeks then 1-2 times weekly long term if required for maintenance of ceruminous ears that may be prone to mixed infections • Can sting broken skin, minimally irritating to intact skin • Cleaner of choice after bathing or swimming to dry ear canals
PAW Gentle Ear Cleaner	Cold pressed citrus oil, milk protein hydrolysates	Pure Animal Wellbeing Pty Ltd, Lane Cove, Australia	• Surfactant ceruminolytic, effective when followed by copious flushing under GA – this is the author's main indication • Should also be effective for removal of purulent exudate with subsequent flushing • Strongly contraindicated where TM is perforated – anecdotally ototoxicity is significant and rapid in onset • No antimicrobial activity published • Claims to 'normalise' ear canals and may therefore be useful in maintenance of chronically affected ears but no published evidence of efficacy for this – used weekly for this purpose • Both these latter claims may be a consequence of activity of cytokines present in colostrum-derived milk proteins • Non-irritant

Table 13.2. Ear Cleaning Products (cont'd)

Product Name	**Declared Composition**	**Manufacturer**	**Comments & Usage Guidelines**
Triz EDTA	533mg Tromethamine (Tris) USP, 141mg edetate disodium dihydrate (EDTA) USP, buffered to pH8 with Tromethamin HCL following reconstitution with 112ml distilled water	Dermapet Inc (Distributed in Australia by Ceva Delvet Pty Ltd, Australia)	• Water based • Non-irritant and middle ear safe though can cause maceration with prolonged use • Efficacious for killing and reducing MIC of *Pseudomonas* mainly, less so other Gram –ve bacteria – use in all cases of otitis where cytology shows mainly rods • Minimal efficacy for cocci or yeast • Has been recommended as maintenance cleaner 1-2 times weekly for dogs prone to *Pseudomonas* otitis but the author would be concerned about the risk for yeast overgrowth in this case • Use as ear flush 10-15min prior to antibiotic administration
Triz EDTA Plus	533mg Tromethamine (Tris) USP, 141mg edetate disodium dihydrate (EDTA) USP, buffered to pH8 with Tromethamin HCL, deionised water, chlorhexidine digluconate (0.15%)	Dermapet Inc *	• Water based • Non-irritant and middle ear safe though can cause maceration with prolonged use • Efficacious for killing and reducing MIC of *Pseudomonas* mainly, less so other Gram –ve bacteria – use in all cases of otitis where cytology shows mainly rods • Some efficacy for cocci and yeast • Use as ear flush 10-15min prior to antibiotic administration
*** Not commercially available in Australia**			

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NOTES:

Chapter 14

Surgical Solutions for Otitis

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ANATOMY

The ear is made up of three parts:

1. The **external ear** consisting of the cartilaginous pinna, and the ear canal itself which is divided into vertical and horizontal portions.
2. The **middle ear** consisting of the tympanic membrane, tympanic bulla and epitympanic recess, and containing the ossicles together with the two muscles associated with them: tensor tympani and stapedius
3. The **inner ear** consisting of the cochlea and semi-circular canals, where signal transduction of sound and balance information to nervous impulses occurs.

PINNA

The pinna appears to have evolved as a device to amplify sound and aid with spectral localisation and in cats, and dogs with upright pinnae, it probably still functions in this way. However in dogs with pendulous pinnae the function is less clear.

The blood supply to the pinna is from the caudal auricular artery which arises from the external carotid artery at the level of the annular cartilage. This artery then sends three branches along the *convex* (medial in the upright pinna/ “outside” in a floppy pinna) surface of the pinna – medial, intermediate and lateral auricular arteries. The concave surface of the pinna is supplied by many small vessels which perforate through foramina in the auricular cartilage from the convex surface. A theory of the aetiology of aural haematoma is that these perforating vessels are disrupted as they pass through the foramina by shearing forces.

AURICULAR CARTILAGE

A good understanding of the anatomy of the auricular cartilage is critical to performing total ear canal ablation (TECA) surgery. The cartilage of the scapha (pinna) is continuous with the cartilage of the ear canal, therefore in order to remove the ear canal and preserve the pinna it is necessary to cut the auricular cartilage, and understanding the areas where this is thicker and folded will enable the surgeon to remove the canal with the minimum of difficulty and create a pleasing cosmetic result.

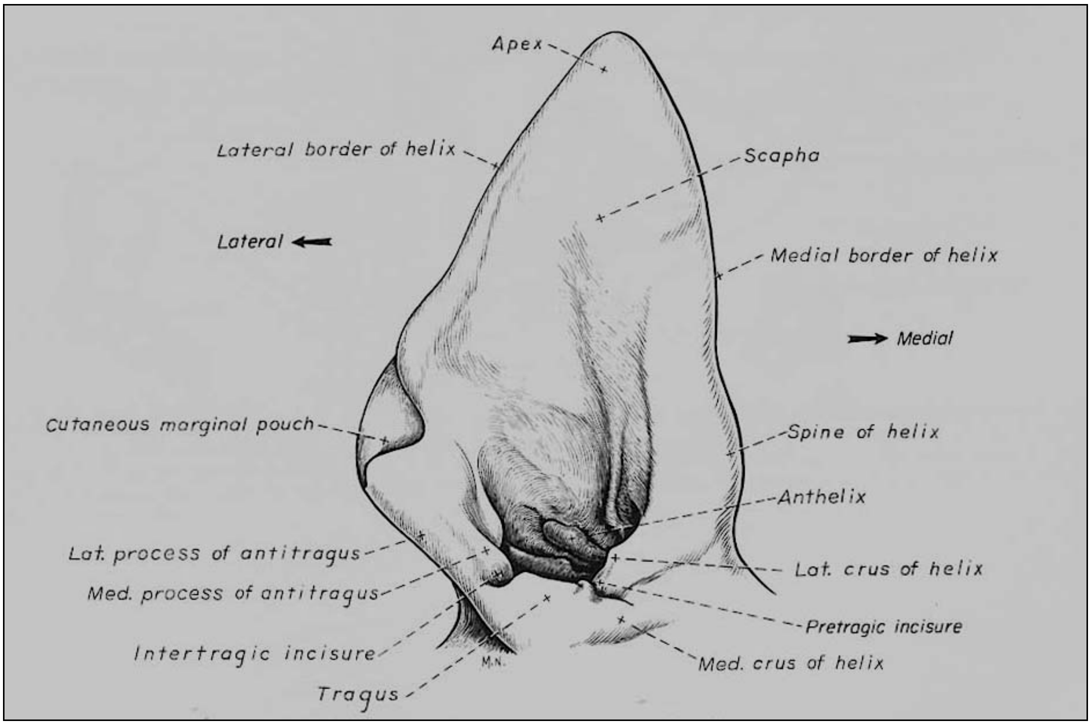


Image 14.1. Right external ear covered by skin (from Millers guide to the dissection of the dog)

The anatomy of the ear canal, and particularly the junction of the auricular with the annular cartilages must be thoroughly understood also to ensure complete removal of all ear canal structures. This will be discussed in more detail in the session on total ear canal ablation surgery.

In cats the ear canal is shorter and the change of direction between the vertical and horizontal components is less marked.

TYMPANIC BULLA

The middle ear contains the means of communication between the external ear canal and the inner ear, mediated by the eardrum and the ossicles. There are also entrances into both portions of the inner ear via the round window (cochlear) and oval window (vestibular). These lie dorsally and approximately opposite the external acoustic meatus; this is important when considering curettage of the bulla during surgery. The auditory (Eustachian) tube also opens into the tympanic bulla and tissue from this area is thought to be the source of inflammatory polyps in cats.

In cats the tympanic bulla is separated by a septum of bone into a small dorso-lateral compartment (adjacent to the tympanic membrane) and a larger ventro-medial section. Sympathetic fibres are present in the middle ear of both species but seem to be rather more prone to damage/irritation in the cat. Horner's syndrome is an almost universal finding after bulla surgery in the cat and is a more common sign of middle ear pathology in cats than in dogs.

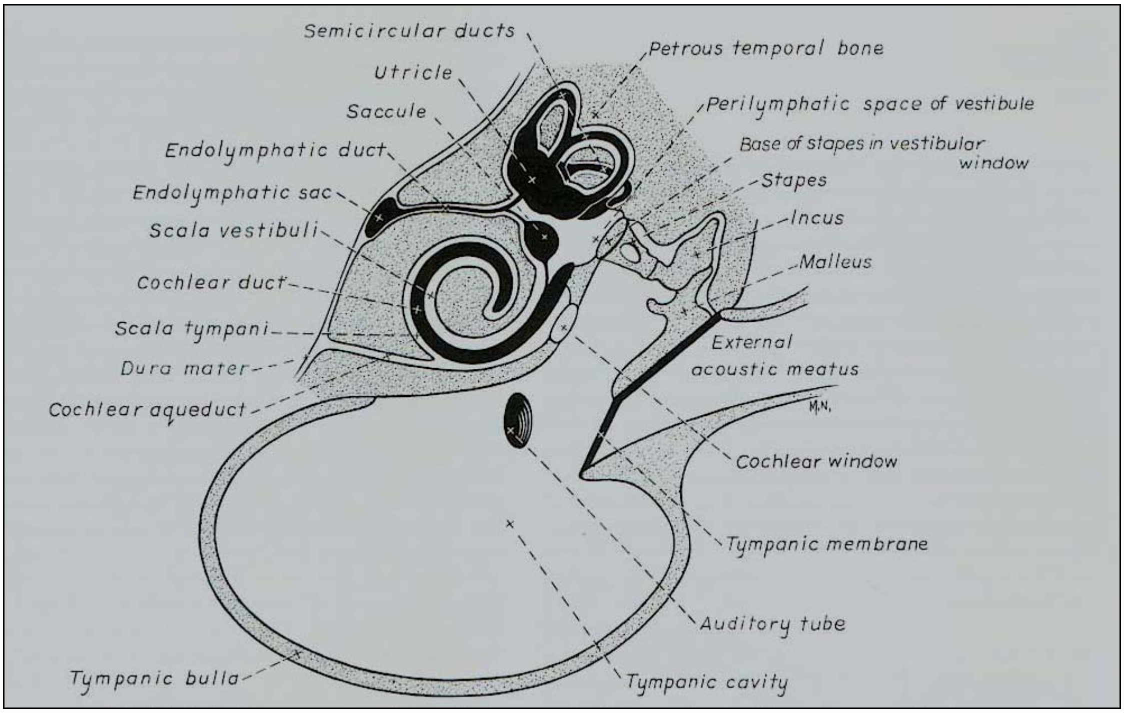


Image 14.2. Schematic section through the inner ear, middle ear and external acoustic meatus of a dog (from Millers guide to the dissection of the dog).

INNER EAR

The anatomy and functioning of the inner ear (despite being fascinating) has little to concern us surgically. Cochlear surgery is not currently performed in dogs other than experimentally.

ANATOMY RELATING TO TOTAL EAR CANAL ABLATION

The course of the facial nerve and vessels encountered which are prone to severe haemorrhage are discussed below.

USE OF ANTIBIOTICS

Surgery is categorised by the degree of contamination into *clean, clean-contaminated, contaminated* and *dirty* and this is helpful in guiding antibiotic use.

Clean surgery: Does not enter gastrointestinal/urogenital/ respiratory tracts, no acute bacterial inflammation encountered, no break in technique.

> *Example:* Incision and drainage of aural haematoma
>
> *Recommended antibiotic use:* None or peri-operative only

Clean contaminated: Entry into GI/UG/Resp tracts without significant contamination

> *Example:* ?Ventral bulla osteotomy for polyp removal (usually associated with infection), vertical canal ablation for tumour removal (if no infection)
>
> *Recommended antibiotic use:* Peri-operative only

Contaminated: Fresh wounds, spillage from GI or UG tracts, major break in aseptic technique.

> *Example:* Traumatic wounds affecting the ear
>
> *Recommended antibiotic use:* Peri-operative only

Dirty: Old wounds, acute bacterial inflammation or pus encountered, "clean" tissues transacted to reach an abscess.

> *Example:* Total ear canal ablation + lateral bulla osteotomy, ventral bulla osteotomy
>
> *Recommended antibiotic use:* Peri- and post-operative antibiotic therapy based on culture and sensitivity results.

In practice, culture and sensitivity information may not be especially helpful once the decision to perform TECA/LBO has been made, and post-operative infection appears to be rare if the surgery is performed correctly. It probably reflects the importance of the environment in perpetuating the infection. Once this "bacteria-friendly" environment is removed by surgery the immune system is quite capable of clearing the infection. I do not routinely use long courses of antibiotics after TECA/LBO, nor do I use "big-gun" antibiotics even where infection with multi-drug resistant *Pseudomonas aerugionosa* has been documented.

ANALGESIA

Ear disease and surgery of the ear canal appears to be profoundly painful. Adequate analgesia is an essential pre-requisite to performing ear canal surgery (particularly TECA/LBO). A multi-modal approach can provide excellent comfort for dogs and cats. A good combination is inject and "splash" a local anaesthetic agent (bupivicaine/lidocaine) into the soft tissues prior to closure, in addition to using a full μ-agonist opiate (e.g. morphine / methadone) pre- and post-operatively and non-steroidal drugs where this can be done safely. In the occasion patient post-operative pain in dogs requires treatment with morphine-ketamine (MK) or morphine-lidocaine-ketamine (MLK) constant-rate infusions. I typically hospitalise patients after TECA surgery for at least one night to assess their discomfort/requirement for analgesia the next day.

BANDAGING

I very seldom use ear bandages. Swelling does not appear to be a particularly big problem after ear surgery and dogs find large bandages around the head uncomfortable. If you do use bandages around the head (e.g. for aural haematoma), make sure that owners and all staff are aware of the position of the pinna. There are occasional anecdotal reports of iatrogenic pinna removal when ear bandages have been removed (under anaesthesia).

DRAINS

Drains can be divided into passive or active ("closed-suction"). The use of drains following ear surgery was common but is now less so. The use of drains in TECA / LBO surgery is not considered beneficial or necessary. I do not routinely use drains after ear surgery except rarely following ventral bulla osteotomy in cats where I occasionally use a passive drain exiting ventrally.

SURGICAL INSTRUMENTS

A selection of specialised instruments are required to perform TECA/LBO surgery. A surgical assistant can also be extremely useful for retraction. Suction with a fine tip (Fraser-Ferguson) is almost mandatory (more so than diathermy) especially if haemorrhage is encountered.

Retractors: Gelpi or West's self-retaining retractors (1-2 pairs). Various sizes required for VBO in cats vs. TECA/LBO in a large dog. Some surgeons like the "Lone Star" self-retaining retractor (originally available from Meadows Animal Healthcare www.avequip.co.uk).

Rongeurs: Small angled rongeurs (Lempert) and occasionally larger double-action rongeurs. Some surgeons like "up-cutting" rongeurs (Kerrison) for bulla osteotomy.

> Periosteal elevator – a "Freer" type is suitable
>
> Selection of osteotomes/mallet
>
> Spraull's needle is very useful for bulla flushing

Selection of curettes – I prefer the kind with a good handle rather than double ended types which look more like a Volkmann spoon.

TOTAL EAR CANAL ABLATION WITH LATERAL BULLA OSTEOTOMY

Indications for Total Ear Canal Ablation

1. Chronic end stage ear disease – clinical defined by:
    a. Calcification of external ear canal
    b. Corticosteroid therapy does not reduce the ear canal stenosis
    c. Permanent loss of tympanic membrane with repeated accumulation of debri with in middle ear
2. Otitis externa/media that has failed to respond to whatever the most intensive medical/dermatological management the owner/dog will tolerate.

    Factors that may influence this:

    a. Owner's financial situation
    b. Owner's willingness to commit time
    c. Owner's compliance with dermatological investigation/treatment (e.g. exclusion diet)
    d. Dog's demeanour and ease of medication
    e. Owner's perception of dog's discomfort
    f. Owner's desire for a "one-stage" solution to ear problems
3. Changes to the ear canal which make it impossible to provide topical medication

    Where otitis has been present for some time and in some particular breeds (e.g. cocker spaniel) there may be marked proliferation and mineralisation of the ear canal which can make it effectively impossible to medicate the ear satisfactorily. In this case it is highly unlikely that it will be possible to resolve the otitis. The role of lateral wall resection in this situation is discussed below.
4. Failure following previous aural surgery (Lateral Wall Resection or Vertical Canal Ablation)
5. Neoplasia of the external ear canal
6. Ear canal trauma

Complications of TECA/LBO

Loss of hearing cannot really be described as a complication as it is reliable and predictable. However it is important to warn owners about this and make sure they understand that their dog may be less traffic-aware and may find it difficult to return to them if they go out of sight (e.g. into a wood). If owners are concerned about hearing loss it is worth pointing out to them that the hearing in such a diseased ear is likely to be minimal anyway.

1. Intraoperative complications
    a. Haemorrhage – Bleeding from the dissection of the ear canal can be relatively profuse but usually stops without specific action as the dissection goes deeper. However, if either of the vessels in the region of the external meatus are traumatised then haemorrhage can be severe and difficult to stop. It can be hard to visualise the bleeding point and ligation is almost impossible. If I encounter brisk bleeding at this point I normally pack the area with swabs and apply firm pressure for ten minutes (by the clock), and then cautiously remove the swab and rexamine. Surgical ligating clips in a small size can be very useful in this area although once again the facial nerve is vulnerable. In the very most severe cases then closing the incision over a swab with planned re-operation to remove the swab and complete the surgery may be necessary.
    b. Technical problems – Some breeds of dog have anatomy which makes the surgery more challenging. The brachycephalic breeds (Bulldog particularly) are not a breed I would choose to do my first TECAs on. The zygomatic process and retroarticular process are very prominent and make the final part of the dissection of the ear canal extremely awkward.
2. Immediate post-operative complications
    a. Facial nerve paresis/paralysis – Unfortunately even with reasonably good technique facial nerve function can be absent after surgery. You must warn owners of this complication. It seems to be of relatively little consequence other than cosmetically, although owners must monitor the eye on the affected side and if necessary apply hypromellose drops to lubricate. Typically the nerve is bruised rather than transected and function usually returns within 4-6 weeks. Although as mentioned above the facial nerve is seldom seen during surgery, it seems clear that the

    incidence of facial nerve injury goes down as experience with the procedure increases.

    b. Vestibular signs – Because this can be such a devastating complication I always warn owners about it. Occasionally post-operatively dogs will suffer from profound vestibular signs which often render them unable to walk and may cause vomiting. This complication seems to be more common if there is incautious curettage in the bulla in the region of the vestibular (oval) window. The signs usually abate within 2-3 days but it is usually sensible to hospitalise these cases if this occurs. Anti-emetic therapy and nutritional support may be necessary.

3. Late post-operative complications
    a. Discharging sinus – These usually appear just caudal to the pinna and can take as long as 2-3 years after surgery to become apparent. They are usually caused by a failure to remove all of the epithelium in the region of the tympanic ring as mentioned above. Re-operation is required. It is usually most helpful to approach the bulla from ventrally and it may be useful to inject a marker such as methylene blue into the sinus tract to aid identification of the epithelial remnant. Try to avoid antibiotic therapy as this will tend to make the sinus harder to find/follow.

Performing the Surgery

As with many surgeries, the technical aspects of performing this surgery are not particularly challenging, and anyone with good general surgical skills should be able to learn to perform this technique. You should make sure you are properly equipped with instruments and suction. It is likely that many complications caused by remnants of epithelium are caused by poor access due to lack of retraction, or poor visibility due to lack of suction or poor lighting.

Pre-Operative Preparation

1. A wide clip is preferred. The eye should be protected from hair clippings with sterile aqueous jelly. The lateral/outer surface of the pinna should be clipped.

2. The skin surface can be prepared with whichever scrub solution is preferred. Although only a very small amount of hearing is preserved after TECA/LBO I still prefer not to instil chlorhexidine into the ear canal: iodine solution is preferred for preparation of this area. It is logical to clean the ear canal – however, I would not delay surgery to get it scrupulously clean and I would prefer it was not full of scrub solution during surgery so “mopping up” as much of the solution with twisted swabs is useful.
3. The animal is positioned in lateral recumbency. It is often necessary to tie the front legs back as they tend to be just where you want to stand.
4. Administer analgesia and antimicrobials prior to beginning surgery. Generally cultures from external ear canal are available prior to surgery and obtained from the tympanic bulla at surgery. I do not delay antibiotic therapy for the purpose of obtaining the culture from the tympanic bulla as typically these dogs are on a range of antibiotics prior to surgery. It is unlikely that a culture obtained directly from the middle ear will yield particularly different organisms from the ear canal.

Surgical Technique

1. Starting on the medial side, make a circumferential incision around the ear canal. Cut dorsal to the knobbly part on the medial side (the *anthelix*) – this makes closure easier. Be careful not to cut deeper than the auricular cartilage medially and damage the skin of the medial side of the pinna. Haemorrhage is normally fairly profuse – this can be reduced with diathermy. It is better to cut the cartilage with a scalpel. On the lateral side, cut the skin 3-5mm ventral to the tragus. At approximately the 4 and 8 o’clock positions the cartilage is very thick and may need to be cut with Mayo scissors or with the scalpel.
2. Using blunt dissection with appropriate tissue scissors (e.g. Metzenbaums), start to free the ear canal from the surrounding tissue. It is easier to get started on the medial side where the tissues are looser. The insertions of various muscles can be seen on the medial surface. Staying as close to the cartilage as possible at this stage minimises haemorrhage. Once a satisfactory “cuff” of cartilage is available, attach an Allis tissue forcep or similar to enable the ear canal to be moved into the desired position. It is useful to be able to apply tension to the tissues to identify where the canal is still attached. Work around the ear canal

staying at all times as close to the cartilage as possible. Gelpi retractors can be used at this stage to aid exposure. By limiting the initial incision to a circumferential rather than T-shaped one, the parotid gland is seldom seen.

3. The key to avoiding complications is to stay as close to the cartilage as possible. Generally the facial nerve is not seen. If you identify it you may wish to retract it carefully using a Penrose drain. With patient dissection, the entire ear canal will be separated from the surrounding tissue. Digital palpation can be used to assess progress by identifying the osseous prominence at the external auditory meatus. In heavily calcified ears this can be confusing.

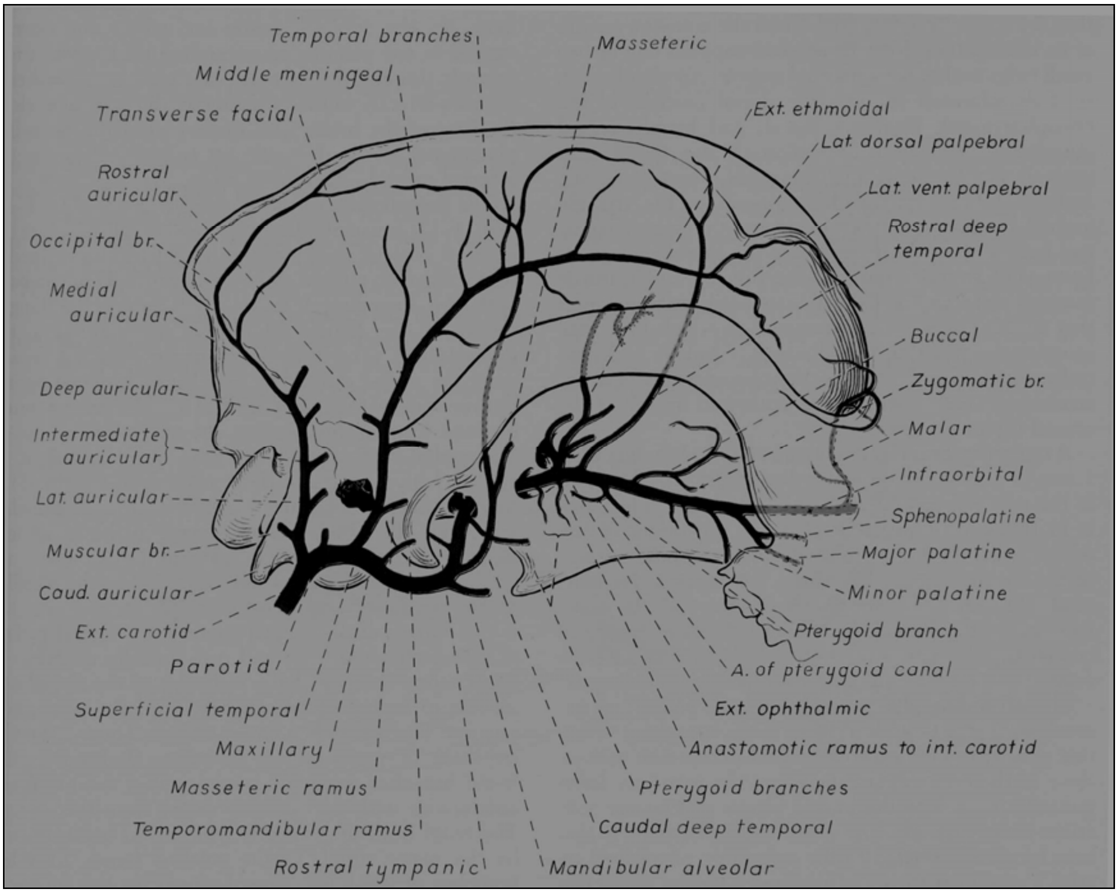
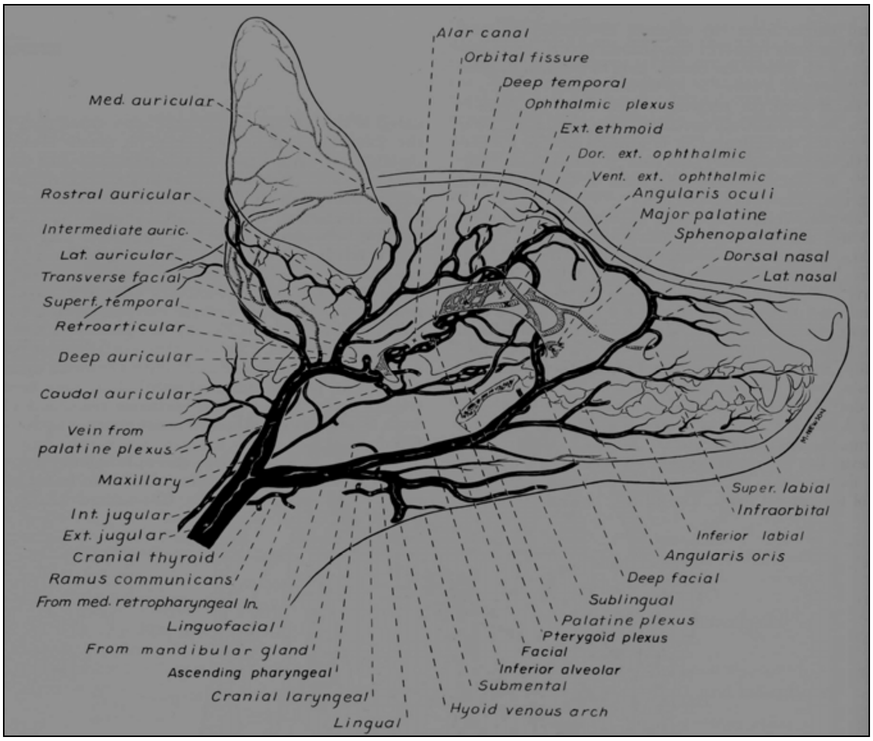


Image 14.3. Arteries of the head in relation to lateral aspect of the skull (from Millers guide to the dissection of the dog).



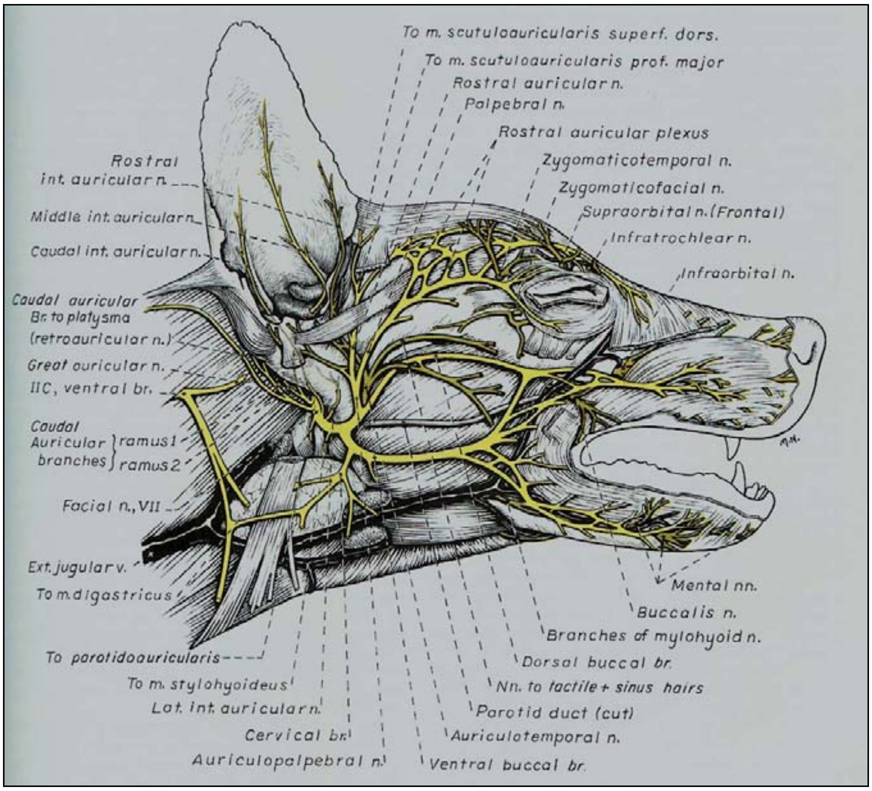


Image 14.4. Superficial veins of the head, lateral aspect.
Image 14.5. Superficial branches of the facial and trigeminal nerves, lateral aspect.
(both from Millers guide to the dissection of the dog)

4. Eventually a point will be reached where the canal is attached to the skull by a ring of epithelium. Transection of the canal is the most hazardous part of the procedure and a solid understanding of where the vulnerable structures are is vital. The facial nerve lies caudoventrally to the canal, exiting the skull at the stylomastoid foramen and continues to hook around the ventral aspect of the canal. If the dissection has been performed correctly the canal and facial nerve should have been separated. The other vulnerable structures are the superficial temporal artery (a primary branch of external carotid a.) and the retroarticular (sometimes called retroglenoid) vein. I normally cut from caudally to cranially with a N0. 11 scalpel blade.

5. Once the canal has been removed, reposition retractors to visualise the external auditory meatus. Using a Freer elevator or similar a thin layer of tissue can be elevated off the bulla surface ventrally. The bulla osteotomy is performed using rongeurs to remove a window of bone from the bulla to enlarge the external meatus. The shape of the osteotomy with the meatus should resemble a keyhole.

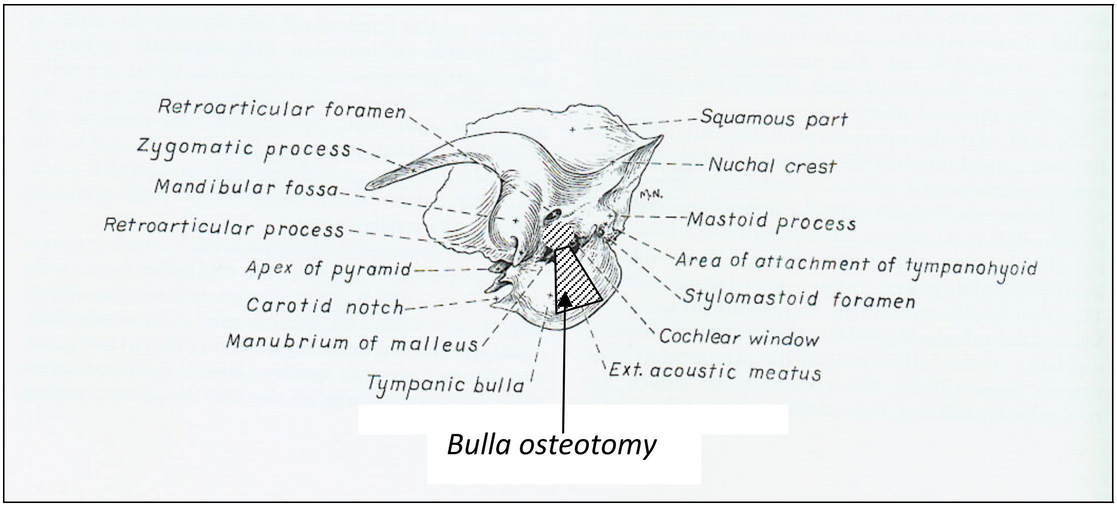


Image 14.6. Left temporal bone, lateral aspect (from Millers guide to the dissection of the dog).

6. Using saline flush, suction and cautious curettage, avoiding the dorso-medial aspect of the epi-tympanic recess, strip out the epithelium from the bulla. In relatively non-chronic cases the epithelium may not be particularly thick or diseased but it is still important to remove this secretory surface to prevent fistulae later on. Often however, the

bulla is obviously abnormal and the epithelium will be thickened and inflamed.

7. The “tympanic ring” or bony external meatus is often the area where small pieces of epithelium are left resulting in complications. Curettage from in to out of the ring is a good way of cleaning off these last remnants. Occasionally a piece of epithelium (still attached) will hide inside the bulla. Flushing is a useful way of making these greyish pieces float into view. Sometimes a small amount of sharp dissection will be needed to detach pieces of cartilage/epithelium in this area but do this with great caution for fear of damaging the vessels or nerves.
8. Once you are satisfied that the bulla is clean (opalescent, glistening bone visible), and the tympanic ring is clear of epithelium/cartilage collect a swab for culture and sensitivity. Consider using local analgesia to improve comfort. This can be injected into the soft tissues or simply used as a “splash-block”. Take care not to inject in the region of the facial nerve.
9. Close the soft tissues using a synthetic, monofilament absorbable suture (Monocryl/Biosyn/PDS). It is difficult to appreciate “layers” as such so I focus simply on eliminating dead space. I bring the edges of my skin incision together in a horizontal linear form, although T-shaped repairs have also been described. The important thing here is to plan the repair to produce as good a cosmetic result as possible for the pinna. The cosmetic result in dogs with overhanging pinnae is usually excellent. However in dogs with erect pinnae, you should warn the owner that the ear carriage can be slightly different.

FURTHER READING

Smeak D.D., Inpanbutr N. (2005) Lateral approach to subtotal bulla osteotomy in dogs: pertinent anatomy and procedural details *Comp Cont Edu Pract Vet* **27**: 377-385

See videos related to this article at
http://vet.osu.edu/SurgeryAnatomyTechniques.htm

LATERAL WALL RESECTION

Indications for Lateral Wall Resection

Lateral Wall Resection has rather a bad press amongst referral practitioners. In contrast, practitioners are often very positive about the role this procedure has. This probably reflects the spectrum of cases seen. Surgeons in referral practice see severely diseased ears that are unlikely to respond to lateral wall resection, and cases where lateral wall resection has failed and are presented for total ear canal ablation. It is important that it is performed before irreversible hyperplastic changes have occurred and unfortunately this is rarely the case. . The aim of the procedure is to improve the microclimate of the ear, to improve drainage and to facilitate medication. It is important to understand that continued medical management is required in most cases. The key point is that lateral wall resection is reserved for particular indications:

1. To improve the morphology of the ear canal
    a. Extremely hairy ears e.g. Bichon Frise
    b. Congenitally small external ear canal opening but before there is marked proliferation/disease. e.g. Shar-peis (this is disputed by some authors)
2. As an *adjunct* to medical treatment in dogs with minimal changes to the ear canal but a propensity to otitis. It is vital that owners understand that they are likely to need to continue medical treatment and that the surgery is designed to facilitate this and reduce the need for TECA/LBO.
3. In very rare cases, to manage ear canal neoplasia if it is affecting the lateral side of the vertical canal (but vertical canal ablation or TECA are likely to be more appropriate).

Lateral wall resection is not a solution on its own to severe otitis and is unlikely to resolve problems in an ear canal with substantial secondary proliferative changes or ongoing infection with multi-drug resistant bacteria.

Complications

Dehiscence post surgery is not uncommon (~27% of cases) due to the contamination of the surgery site. The most common complication of ear canal resection is ongoing otitis externa and progression of the secondary changes in the ear canal. Only 30-50% of dogs benefit from this procedure and the poor results are usually due to performing the surgery too late. Pre-existing pathology that results in failure of the procedure include proliferative dermatitis of the medial wall of vertical canal, pathology in the horizontal canal (stenosis, obstruction), failure to diagnose tympanic membrane rupture and otitis media and severe proliferative mucosal disease with calcification of the auricular cartilage. Other causes of failure include making the "washboard" too narrow with constriction at its base, failure of the procedure to adequately drain the horizontal canal, failure to recognize and treat any underlying disease (hypothyroidism, primary ideopathic seborrhoea) and middle ear disease.

Surgical Technique

Pre-operative ear clean and systemic antibiotics are recommended for 10 days before surgery. Parallel skin incisions are made which are 1.5x the length of vertical canal to extend to at least 1cm ventral to floor of the ear canal. A short dorsal subcutaneous incision is made down to the auricular cartilage and the subcutaneous tissue is blunt dissected off the auricular cartilage preserving the parotid salivary gland. Rostral and caudal full thickness cuts are made in the cartilage using scissors, starting from intertragic (lateral) and pretragic fissures (medial), distally to the annular cartilage. A large vein crosses the tragus in cats and requires ligation. The cartilage flap is trimmed to 1/3-1/2 of its length and folded distally to form a "washboard". The cartilage is sutured to the skin using a nonabsorbable monofilament suture with the edges apposed under minimum tension.

VENTRAL BULLAE OSTEOTOMY

Lateral bulla osteotomy is performed as part of a total ear canal ablation and is discussed above. Ventral bulla osteotomy without ear ablation can be performed to treat otitis media and inflammatory polyps in cats. It is more commonly performed in cats as they have a lower prevalence of otitis externa than dogs and ear ablation less commonly performed. The advantages of ventral bulla osteotomy compared to lateral bulla osteotomy include improved exposure, more consistent ventral drainage of the tympanic bulla, the ability to approach both bullae if there is bilateral disease and a lower likelihood of iatrogenic facial nerve injury.

Complications

Potential complications associated with ventral bulla osteotomy include hypoglossal nerve paresis, Horner's syndrome, vestibular disease and inadequate drainage with continued otitis externa.

Surgical Technique

A paramedial skin incision is made just medial to the mandibular salivary gland centred midway between angular process of mandible and the wings of the atlas. The centre of the incision is level with the external auditory meatus. The underlying platysma muscle is incised and blunt dissection is continued between the digastric muscle (medial to it) and stylo/hyoglossal muscles. The hypoglossal nerve is located on the lateral aspect of the hypoglossus muscle and followed down to the bulla. The tympanic bulla is easily palpated in cats but palpation is more difficult in dogs. The hyoid apparatus can be palpated with the stylohyoid attaching lateral to the midpoint of the bulla. The bulla is identified in the angle between the hypoglossal nerve/lingual artery and the maxillary artery. The muscle fibres over the bulla are separated and retracted with Senn retractors. A Steinmann pin on a hand chuck is used to penetrate the bulla and the stoma enlarged with rongeurs. A bone curette is used to remove the epithelial lining of the bulla, being careful with the dorsal aspect. In cats the tympanic bulla is divided into *ventro-medial* and *dorso-lateral* compartments and both compartments need to be opened. When the ventral compartment of the bulla is opened, the bony plate on the floor of dorsal compartment is opened as well to expose the dorsolateral compartment. The bulla is lavaged with sterile saline prior to routine closure of the incision.

FELINE INFLAMMATORY POLYPS

Inflammatory polyps are a common, benign masses which are thought to arise from the epithelial lining of the auditory tube or the tympanic bulla. From this area they can grow laterally into the external ear canal, cranio-medially into the nasopharynx, or very rarely both into the ear and pharynx together.

The cause of these masses is unknown but various aetiologies including congenital causes and response to viral infection have been proposed. Many cats will have a bacterial otitis externa/media at the time of presentation but whether these infections are purely seconday or are involved in the appearance of the polyp is not known.

Clinical Signs

Affected cats are usually young (median in one study 24 months), and polyp appearance often follows an episode of upper respiratory infection. However, any age of cat can be affected. No breed or sex predilection has been reported.

Presenting signs depend on the site of the polyp but stertor, dyspnoea, sneezing, gagging, dysphagia or halitosis might suggest a nasopharyngeal polyp whereas otorrhoea and odour from the ear are common signs of a polyp in the external ear canal. Not all cats will have neurological signs, but a significant proportion will present with a head tilt, ataxia or Horner's syndrome. Non-specific signs of weight loss or inappetence may also be present.

Diagnosis

Aural: A pink, fleshy mass in the ear canal of a young cat gives a high suspicion of a polyp. Other tumours, especially lymphoma and ceruminous gland adenoma/adenocarcinoma should be considered.

Nasopharyngeal: The polyp may not be immediately visible on oral examination and it may be necessary to palpate the palate or use a spay hook or retroflexed endoscope to evaluate the nasopharynx.

Once a suspected polyp has been identified, imaging to evaluate the tympanic bullae should be performed. Plain radiography is likely to be approximately 75% sensitive for involvement of the middle ear. CT or MRI (where available) could be used although they can be costly.

Treatment

Early publications emphasised the role of surgery (ventral bulla osteotomy), perhaps reflecting a bias to referred/recurrent cases; however, a study from Cambridge published in 2000 suggested that a high proportion of cats with nasopharyngeal polyps were cured by simple traction, and that traction of polyps in the external ear canal combined with prednisolone (tapering dose for four weeks) was also curative in a proportion.

Therefore, surgery is not typically offered as a first line treatment. It may be considered more quickly in cases where neurological signs are present. In the Cambridge study, the presence of radiographic changes in the bulla did not prevent simple traction being effective. In a separate study from Colorado, bulla involvement was predictive of recurrence following traction. However, steroids were not administered in these cases.

Polyps are usually pedunculated. Following traction, a characteristic "tail" to the polyp is a reassuring sign that the entire polyp has been removed, although the predictive value of this finding has not been studied.

Summary of treatment recommendations once a polyp has been identified.

1. Perform a clinical evaluation and document whether neurological signs are present.
2. Perform imaging to evaluate the tympanic bullae.
3. If either neurological signs are present or the bullae appear affected then ventral bulla osteotomy might be warranted as a first line treatment although there is little evidence for this.
4. Remove the polyp by traction. If it is clear that the polyp has been incompletely removed then consider ventral bulla osteotomy to complete removal.
5. Treat the cat with a tapering dose of prednisolone over four weeks starting with 1mg/kg daily for two weeks.
6. If the polyp recurs, perform a ventral bulla osteotomy, although further traction/steroid treatment may be effective.

FURTHER READING

Donnelly K.E., Tillson D.M. (2004) Feline Inflammatory Polyps and Ventral Bulla Osteotomy *Comp Cont Edu Prac Vet* **26:**446-454

A useful review of the subject although some may feel the role of VBO is over-emphasised.

Anderson D.M., Robinson R.K., White R.A.S. (2000) Management of inflammatory polyps in 37 cats *Veterinary Record* **147:**684-688

A case series from Cambridge in which an apparent response to a tapering course of prednisolone was identified.

NOTES:

Chapter 15

Interactive Case Sessions: Otitis

Greg Burton FACVSc (Dermatology)
Arthur House BSc BVMS PhD Cert SAS Dip ECVS MRCVS
David Robson FACVSc (Dermatology)
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Chapter 16

Pruritus: Differential Diagnoses and Diagnostic Approach – Part 1

Mandy Burrows
BVMS MACVSc FACVSc Vet Dermatology

INTRODUCTION

The diagnosis of pruritic disorders is not always easy in the cat. Cats often groom rather than scratch and in many cases, owners do not believe that the cat is pruritic because they have not seen any evidence of scratching. In addition, some owners fail to recognise excessive grooming as a sign of pruritus and often pruritus is not the reason for the consultation. Some owners may actually cite alopecia as the reason for presentation assuming the hair loss to be spontaneous. Others may be concerned about the presence of an eosinophilic plaque which develops from repeated licking in one area. Owners do not suspect that such problems are self induced, particularly if the cat hides when it overgrooms. One of the challenges to the clinician is to persuade owners that such lesions can be self induced and not a spontaneous problem.

HISTORY

The following information should be obtained

1. **Breed:** Persians are predisposed to dermatophytosis and also because of their nose and lacrimal duct conformation to superficial bacterial pyoderma and fungal (e.g *Malassezia* spp) skin infections. Urticaria pigmentosa has, to date, only been observed in Sphinx and Devon Rex cats. Self induced non inflammatory alopecia of behavioural origin is more common in Siamese, Abyssinian and Burmese breeds.
2. **Age of onset:** the appearance of pruritus in a cat under 6 months would suggest either a parasitic dermatoses (e.g Notoedric mange, Cheyletiellosis), dermatophytosis or flea allergy dermatitis, whereas pruritus in a cat between 8 months and 3 years of age would suggest an allergic dermatitis (adverse food reaction or atopic dermatitis) and

in an older cat, a pruritic exfoliative erythroderma may suggest cutaneous epitheliotropic lymphoma.

3. **Lifestyle and environment**: cats living together in groups, breeding colonies or rescue premises are predisposed to contagious dermatoses; dermatophytosis due to *Microsporum canis* and pruritic ectoparasitic infestations. These cats are also more exposed to flea infestations and therefore more inclined to develop non inflammatory alopecia related to flea allergy dermatitis. It is relevant to assess the individual character of the cat; nervous, introverted, shy or socially inferior cats are predisposed to psychogenic alopecia; any cat faced with territorial or psychologic stress may develop a psychogenic dermatosis. Classic examples include rival or aggressive companions, moving house, a new baby or pet in the household or the loss of a close companion.
4. **Previous illness:** an association between gastrointestinal problems and overgrooming may be suggestive of an adverse food reaction.
5. **Progression of signs and seasonality:** seasonal pruritic dermatoses may suggest a pollen or flea bite allergy.
6. **Response to prior therapy:** the response to corticosteroids is usually good for self induced alopecia arising from flea bite hypersensitivity dermatitis, atopic dermatitis and early adverse food reaction; partial or poor in chronic adverse food reactions and behavioural disorders and poor in dermatophytosis and ectoparasitic infestations such as demodicosis.
7. **Evidence of contagion**: it is useful to establish whether or not any member of the household has cutaneous lesions as these may represent a zoonosis, usually of flea origin, although *Cheyletiell*a may also be zoonotic. Multiple animal involvement strongly suggests a contagious dermatosis; dermatophytes, fleas, *Otodectes cynotis* and *Cheyletiella blakei* should be considered.

CLINICAL EXAMINATION

General clinical examination: is concerned with signs associated with atopy (e.g conjunctivitis, rhinitis, allergic bronchitis) and physical signs of a behavioural disorder (e.g tachycardia, polyphagia, obesity, excess salivation, diarrhoea and poor grooming). In my experience cats with chronic pruritus are often lethargic and in the absence of pyrexia this is of no diagnostic significance.

The dermatological examination: is concerned with assessing the **degree of pruritus** and the **type and distribution of lesions.**

In cats: four main **types of presentations** are seen either alone or combined in pruritic cats.

1. Miliary Dermatitis

Miliary dermatitis is characterised by a small, erythematous, **crusted papules** that are usually non-follicular in distribution. Miliary dermatitis **is not a diagnosis** but rather a **descriptive term.** The differential diagnosis is extensive; the most common being **allergies**, **ectoparasites** and **infections** (Table 16.1). Immune mediated diseases such as pemphigus foliaceus may occasionally mimic a miliary dermatitis.

Table 16.1. Causes of Papulocrustous (miliary) Dermatitis in the Cat

Mechanism	**Aetiological Agent or Disease**
Ectoparasites	*Notoedres cati* *Cheyletiella* *Demodex* spp. *Otodectes cynotis* *Sarcoptes scabiei*
Allergic skin disease	Flea bite hypersensitivity Mosquito hypersensitivity Food hypersensitivity Atopy
Infectious organisms	Superficial pyoderma Dermatophytes *Malassezia* dermatitis
Neoplasia	Mast cell tumour Epitheliotropic lymphoma Urticaria pigmentosa
Immune-mediated	Pemphigus foliaceus Pemphigus erythematosus Cutaneous drug eruptions

2. Self Induced, Symmetrical Non-Inflammatory Alopecia

Non inflammatory alopecia is used to describe an acquired syndrome of multifactorial aetiology that results in loss of hair over the perineum, proximal ventral and ventro-lateral tail, hind limbs, ventrum, lateral abdomen and distal forelimbs and on rare occasions extends to the lateral thorax (Table 16.2). The dorsum is not usually affected and the skin does not appear inflamed.

Feline non-inflammatory alopecia may be **self inflicted** from licking, biting or pulling the hair as a result of pruritic dermatoses or conditions causing psychogenic disturbances or it may result from **spontaneous hair loss** due to either epilation of hair or hair shaft fracture. Most, if not all, such cases are the result of pruritus or self-trauma due to an underlying problem, and are not related to sex steroids or other hormones.

Table 16.2. Causes of Symmetrical, Self-inflicted Alopecia in the Cat

Mechanism	Aetiological Agent or Disease
Ectoparasites	Cheyletiella Demodex spp. Otodectes cynotis
Allergic skin disease	Flea bite hypersensitivity Food hypersensitivity Atopy
Infectious organisms	Dermatophytes
Psychogenic	

3. Eosinophilic Dermatoses (Eosinophilic Granuloma Complex)

The new term feline eosinophilic dermatoses has been proposed to cover the group of skin diseases previously referred to as eosinophilic granuloma complex (EGC). The term ECG is not a specific disease but a reaction pattern which includes a group of disorders affecting both skin and mucous membranes subdivided into **eosinophilic ulcer**, **eosinophilic plaque** and **eosinophilic (collagenolytic/linear granuloma)** (Table 16.3). These different clinical lesions often occur in the same patient and may respond to the same type of therapy. They should be thought of as different reaction patterns within the same disease process. Although the lesions are clinically distinct, it is believed that feline allergic dermatitis is most often the underlying cause. However, a small percentage of cases may occur as a result of eosinophil dysregulation. Regardless of which clinical lesion is present, begin a thorough allergic evaluation of your feline patient in cases where the lesions are chronic, recurrent or refractory.

Table 16.3. Underlying Causes of Feline Eosinophilic Granuloma Complex

Mechanism	Aetiological Agent or Disease
Allergic skin disease	Flea bite hypersensitivity Adverse food reactions Mosquito hypersensitivity Atopy
Infectious organisms	Superficial pyoderma
Others	Genetic Idiopathic

4. Erosive and Crusting Dermatosis of the Face and Neck

These cases are usually markedly pruritic. Many of these cats inflict severe excoriations and the skin conditions often appear striking and spectacular.

Table 16.4. Causes of Facial Pruritus in the Cat

Mechanism	Aetiological Agent or Disease
Ectoparasites	Notoedres cati Cheyletiella Demodex spp. Otodectes cynotis Sarcoptes scabiei
Allergic skin disease	Flea bite hypersensitivity Food hypersensitivity Atopy
Infectious organisms	Superficial pyoderma Dermatophytes Malassezia dermatitis
Neoplasia	Mast cell tumour Epitheliotropic lymphoma
Immune-mediated	Cutaneous drug eruptions
Psychogenic	

DIAGNOSTIC APPROACH

The clinician must now decide whether the cat is truly pruritic or if the cat is exhibiting a stereotypic behaviour pattern of excessive grooming (psychogenic dermatitis). The latter condition is rare. Though we can identify several specific causes of pruritus in the cat, bear in mind that in any individual cat the clinical picture may represent a combination of several different aspects. This combination may include both pruritic and behavioural aspects in some cases.

Step 1. Does This Cat Have a Mite Infestation?

A coat combing and multiple superficial and deep skin scrapings should be performed to evaluate for ectoparasites (e.g. fleas, flea faeces, *Demodex*, *Cheyletiella*, *Otodectes*, *Notoedres and Sarcoptes* species). If the tests are positive, the cat should be treated for the specific disease identified. *Cheyletiella blakei* infestation is common in long haired cats and possibly under diagnosed as a cause of traumatic alopecia. The degree of pruritus can be variable between infested cats. The most common clinical presentation is a papular rash and scale, mainly along the dorsum, but some cats may only show alopecia or may be totally asymptomatic.

Otitis or pruritus involving the head in any animal is a clear indication for performing an ear smear. This technique is used primarily to find *Otodectes cynotis* and other species of ear mites. Occasionally *Demodex* mites may be found. The pruritus from ear mite infestations is believed to be due to mechanical irritation and hypersensitivity reaction; do not discount the finding of one mite or egg especially in intensely pruritic adult animals; many species of ear mites migrate to the ear margins to deposit eggs, therefore if swabs from the ear canal are negative; skin scrapings from the ear margins or periaural skin are indicated.

Notodres mites are usually relatively easy to locate on skin scrapings but *Demodex*, *Cheyletiella*, *Otodectes and Sarcoptes* mites can be more elusive. If there are no mites seen in skin scrapings and coat brushings then we implement an acaricidal trial using selamectin 6mg/kg applied topically q 14 days for three treatments on all affected and in contact animals. Selamectin is not licensed for this purpose but when applied using this dosage regime is effective at eliminating infestation with *Notoedres cati*, *Sarcoptes scabiei*, *Otodectes cynotis* and *Cheyletiella blakei*. It is not effective at eliminating infestation with either *Demodex* species and the clinician needs to remember that this mite has not been reliably eliminated from the differential diagnoses list at this stage.

Step 2: Does This Cat Have a Dermatophytosis?

A Wood's lamp examination should be performed. When present, fluorescent hairs should be plucked for fungal culture. If the Wood's lamp examination is negative then a sample should be obtained with a toothbrush and submitted for fungal culture. This technique involves brushing the cat's entire hair coat with a new toothbrush and submitting it to the laboratory in its original wrapper. Make sure to brush the entire hair coat thoroughly until the bristles are full of hair or the cat has been combed for at least one minute. It is important to brush the non-lesional part of the body initially and the alopecic region last. This serves two purposes; firstly it **minimizes the chance that tooth brushing mechanically spreads spores over the body**; secondly, if cultured last, **spores are present in the largest numbers on the tips of the bristles**.

Step 3. Does This Cat Have a Bacterial or Yeast Infection?

Evaluation of cytology is a cheap, simple and rapid method of assessing for the presence of bacteria and yeast in superficial skin infections and otitis externa. For **impression smears** we rub or press a glass slide onto the surface of the lesion or exudate. This works extremely well when the skin is greasy or exudative. Do not exert too much pressure or the slide may snap. Ulcers and the surface of "pricked" papules and pustules may also be sampled in this fashion. **Sampling with a cotton bud** is useful if the skin is dry and is the method of choice for evaluating the external ear canal. Moisten with saline solution, rub on the surface of affected skin and then roll the tip onto the glass slide. Using **clear sticky tape** is also a useful technique. The type of tape used is very important because there is a marked variation in degrees of adhesiveness and transparency between brands. Press tape sticky side down repeatedly onto the lesional skin surface until it loses its adhesiveness. This means that it is covered in corneocytes. Stick one end of the tape onto a glass slide to facilitate staining. When assessing cytological specimens it is important to scan at low power initially and then under oil immersion and assess for presence or absence of inflammatory cells, organisms and keratinocytes.

Step 4. Does This Cat Have Flea Allergy Dermatitis?

If the skin scrapings and Wood's lamp examination are negative, then we usually implement a thorough flea control program to evaluate for the diagnosis of flea allergy dermatitis (FAD). In Australia, FAD is undoubtedly the major cause of miliary dermatitis and non inflammatory alopecia in cats and should always be evaluated before more extensive diagnostic investigation is undertaken. There is no breed, age or sex predilection reported for FAD in the cat but in our experience flea allergy often affects young cats of 6 months of age or older. The pruritus may be seasonal or non seasonal depending on the geographic region.

Pruritus is moderate to severe. The lesions are usually associated with papulocrustous eruptions with alopecia, excoriations, crusting and scaling confined to the dorsal lumbosacral region, caudomedial thighs, ventral abdomen, flanks and neck but lesions may become generalised. Pigment changes may occur and multifocal, small, melanotic macules are evidence of previous inflammatory sites. FAD cats may also present with self-induced symmetric alopecia and eosinophilic granuloma complex lesions. There is sometimes a moderate to marked peripheral lymphadenopathy.

The presence of fleas, flea faeces or flea eggs may be demonstrated during the physical examination and in coat brushings although in many instances it is impossible to find definitive evidence of flea infestation which probably reflects the grooming activity and prompt removal of fleas by affected cats. Other supportive evidence includes the presence of *Dipylidium caninum,* the presence of fleas or flea faeces on in-contact animals, the presence of zoonotic lesions on members of the household and the lack of suitable flea control on a cat that leads an indoor/outdoor lifestyle and is in regular contact with other cats in the neighbourhood.

Though the presence of flea and/or flea excreta in the hair coat is a strong indication of underlying FAD, the clinician should be aware that a lack of gross flea presence does not negate the diagnosis as affected cats often quickly remove any evidence of fleas. In many cases, response to flea eradication measures is the best confirmation of a putative diagnosis of FAD.

As previously discussed we call this a "flea therapeutic trial" and confirmation of the diagnosis is made by clinical response to flea control. The time taken for clinical improvement depends on the severity and chronicity of the disease, the degree of hypersensitivity and the magnitude of the flea challenge. As a general rule the response (or lack thereof) of a therapeutic trial is assessed at four to six weeks. In the cat we usually use either fipronil spray 6ml/kg or fipronil TS applied topically q 7 days or oral nitenpyram 1mg/kg q 48 hrs. In chronic or severe cases we will combine these modalities. Glucocorticoids should not be prescribed at this stage because they will mask the response to the trial.

Interpretation of the "Flea Therapeutic Trial"

A **good response** (>80% improvement) is consistent with the diagnosis of FAD. A long term maintenance flea control program is then instituted and the patient assessed for ongoing response.

A **moderate response** (30-80% improvement) warrants continuing the therapeutic trial for a further 14 to 21 days and then reassessing the patient. If there is no further response (still 30-80% at day 42) there may be concurrent disease eg FAD and feline atopic dermatitis.

A **poor** response (< 30% improvement) suggests the diagnosis of FAD is unlikely and further investigation of other causes is warranted.

Step 5. Does This Cat Have a Food Allergy?

At the same time we commence a "flea therapeutic trial", we usually begin an elimination diet trial to investigate the possibility of an **adverse food reaction** (AFR). No sex predilection has been reported for AFR in cats. Although an AFR can occur in any breed of cat, the Siamese cat has been reported to be at risk. The age of onset of pruritus due to an AFR in the cat ranges from 6 months to 11 years with a mean of 4 to 5 years.

The most common clinical sign of AFR in cats is a non seasonal pruritus which is most commonly localised to the face, including the preauricular, ear pinnae, neck and periorbital region. Other less commonly affected regions include the limbs, ventrum, paws and perineum. A concurrent bilateral ceruminous otitis externa is often present. The most common lesion observed in cats with AFR is a miliary reaction pattern accompanied by varying erythema, alopecia, erosions and crusting. Other common cutaneous reaction patterns include symmetrical alopecia and eosinophilic granuloma complex lesions (eosinophilic ulcer and eosinophilic plaques). Less common cutaneous clinical signs associated with AFR in cats include angioedema and urticaria.

Gastrointestinal tract symptoms including vomiting, diarrhea and lymphoplasmacytic colitis are reported to occur in some cats with cutaneous signs of AFR. In cats, diagnosed with AFR, 21% to 30% are reported to have concurrent cutaneous hypersensitivities including atopy and flea-bite hypersensitivity.

The diagnosis of canine and feline AFR is based on feeding an elimination diet and documenting the resolution of clinical signs followed by a demonstrated relapse of clinical signs after the introduction of the previously fed foods (provocative challenge). Intradermal testing, ELISA and RAST in vitro allergy testing and gastroscopic food testing are not reliable for the diagnosis of AFR in dogs and cats.

The primary objective is to select a protein source that has no history of previous exposure and possible options include kangaroo, horse, donkey, camel, goat, turkey, duck, emu and rabbit meat. We do not use a carbohydrate source such as potato or pumpkin as this is often unpalatable for cats. Home cooked diets are preferable to commercial diets, in my opinion. Commercial novel protein and hydrolysate diets are however nutritionally balanced, very easy to use and do ensure client compliance. If no response is observed using a commercial diet, however, it is difficult to completely rule out the diagnosis of AFR. The cat should be confined inside during the elimination diet to prevent hunting and feeding at neighbour’s houses. The diet should be fed for a minimum of eight weeks.

A diagnosis of AFR is confirmed by demonstrating that the clinical signs recur when previously fed foodstuffs are re-introduced. This is achieved by feeding a test meal of the cat’s previous diet including treats for 10 to 14 days. Some owners will refuse to a challenge with the former food after reduction in clinical signs, but it is important to underline the importance of the challenge test, because a significant placebo affect can occur in 20% of cases. This means that continuing the elimination diet will be useless in some patients. When the clinical signs will reappear is a subject of debate. Most authors agree that the animal should relapse within 4 to 72 hours although longer periods (up to 10 days) have been recorded.

The offending allergens then can be identified by a sequential challenge diet in which single ingredients (fish, beef, dairy, pork, chicken, lamb/mutton, eggs, wheat) are introduced to the elimination diet once a week to determine which individual allergen or allergens is incriminated. In our experience, most cats are only allergic to a single protein.

On the basis of information obtained from the sequential rechallenge, a commercial food that does not contain the offending substance can usually be selected. Canned diets require fewer preservatives than dry foods and may therefore be better tolerated. About 30% of cats, however, **cannot consume any commercial diet** and must be maintained on a home prepared diet. These animals must be maintained on a balanced home-cooked diet with additive free vitamin and mineral supplements. Prolonged feeding of a single protein source may increase the likelihood of developing an adverse reaction to that protein. It has been suggested that this occurs more commonly in cats than in dogs. Usually changing to an alternative diet with a different protein and carbohydrate source will stabilise the case. In this context the hydrolysate diets have a theoretical advantage as the individual should not mount and allergic response to the hydrolysed proteins.

Step 5. Is This Cat Atopic?

If there has been no response to the elimination diet then the cat should be evaluated for feline atopic dermatitis. In cats, lesions are generally found on the face, rarely on the feet, and occasionally generalised. Pruritus, typified by erythema, alopecia and hyperpigmentation is the most frequent sign. Miliary dermatitis and the eosinophilic granuloma complex have also been reported as being secondary to atopic dermatitis. Atopic cats are prone to secondary infections with *S intermedius* and *Malassezia pachydermatis,* and *Malassezia* otitis externa is a common complication of feline atopic dermatitis in our dermatology practice. Age of onset, breed or sex predilections for feline atopic dermatitis have not been well defined in cats.

A clinical diagnosis of atopy should be made on the basis of a compatible history in conjunction with ruling out an adverse food reaction and flea bite hypersensitivity dermatitis. Intradermal allergy testing is performed to select the allergens for an immunotherapy regime and to implement allergen avoidance measures. It is more technically demanding to perform in the cat than in the dog and will require referral to a veterinary dermatologist. If an owner elects not to pursue intradermal allergy testing then the most appropriate course of action is to commence symptomatic medical therapy. Recommended treatments for feline atopy include allergen specific immunotherapy, allergen reduction, cyclosporin, glucocorticoids, antihistamines and fatty acids. In our practice we often use cyclosporin at 5mg/kg q 24hrs with immunotherapy for the management of atopic cats.

If the testing is negative or the cat fails to improve with symptomatic therapy for presumptive atopic dermatitis then several possible diagnoses remain; in a cat with persistent miliary, erosive to ulcerative facial dermatitis or eosinophilic granuloma complex lesions then it is worthwhile to consider collecting a skin biopsy for histopathological evaluation to rule out an immune mediated or neoplastic skin disease. In cat with persistent non-inflammatory alopecia then it is worthwhile at this stage to consider the possibility of psychogenic alopecia. Histopathological evaluation of a skin biopsy may be of value in this instance as well.

Step 6. Could This Cat Have Psychogenic Factors Contributing to the Overgrooming?

In our dermatology referral practice, psychogenic alopecia is uncommon as a sole primary clinical entity in the cat. Assessing how often cats with primary pruritic skin disease develop a stereotypic component to their overgrooming, however as part of the disease process can be difficult. In some cases the initial pruritic trigger may no longer be present and identifiable but overgrooming has become self reinforcing. Some individual cats have a temperament that predisposes to this outcome. The possibility of both a pruritic component combined with a psychogenic component should be considered in some cases. We would estimate that 10% to 15% of cats with chronic non inflammatory alopecia in our referral dermatology practice have a psychogenic component reinforcing a primary pruritic skin disease. This may account for the partial success seen in some cases with symptomatic anti pruritic therapy. No single diagnostic test can confirm psychogenic alopecia.

Cats that are typically affected include the Siamese, Burmese, Abyssinian and Himalayan breeds. The primary abnormality is thought to be **excessive grooming** that may result from an **anxiety neurosis**. The anxiety may be caused by **psychological factors** such as displacement phenomena; eg. a new pet or baby in household; a move to new surroundings, boarding, hospitalisation, loss of a favourite bed or companion, or competition for a social hierarchy position with other pets in the household or in response to other cat's entering the affected cat's territory.

Lack of improvement in either cutaneous or behavioural signs after drug treatment of any sort is of no diagnostic value. Equally the efficacy of corticosteroids or synthetic progestagens cannot be used to conclude that a hypersensitivity skin disease is present. For instance, megoestrol acetate has marked neuroleptic activity and conversely many of the psychotropic drugs have sedative or antihistamine activity. An accurate diagnosis of feline psychogenic alopecia involves a **complete diagnostic work-up** as this condition is diagnosed primarily by **ruling out all other differential diagnoses.**

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NOTES:

Chapter 17

Pruritus: Differential Diagnoses and Diagnostic Approach – Part 2

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INTRODUCTION

Pruritus is extremely common in general practice and pruritus in the dog has many potential causes. Each individual dog may have more than one cause of itch. Pruritus in dogs is most effectively managed when the cause is known. Pruritus is one of the most frustrating aspects of dermatology. Each of us is very familiar with the physical damage that constant scratching causes, but many dogs with chronic itch can also have personality changes that exacerbate the problem. And if they don't have personality changes, their owners surely do! The case of each client and pet should be approached individually, as there is great variation in how much pruritus each client and pet can tolerate. It is useful to determine the level of itch for each patient, as that determination will allow us to develop a short list of potential causes which then enables us to develop a rational diagnostic and treatment plan. Most dogs with pruritic skin disease will have diseases that are manageable, not curable. And for most dogs, we can decrease itch but not ablate it. Acknowledging these facts ourselves and helping our clients accept these facts will allow us to have an impact on canine pruritus, one patient at a time.

STEP 1: GET A GOOD HISTORY

Taking a standardised history is very important. Because some owners are better oral historians than others, a dermatology history questionnaire is immensely helpful. If you have a clinic website, you can have these forms available on line and ask your clients to download and fill them out before they come for the consultation; alternatively the clients can fill them out while they wait to be seen. You can make this task easy by asking your client to circle or tick appropriate responses. A copy of the questionnaire we use in our clinic is included at the end of these notes.

When assessing the distribution, the clinician should avoid asking the question “where does the dog scratch?” this usually yields incomplete information. Instead the client should be asked more specific questions which usually provides more accurate information.

Does the pet rub or scratch its face, nose, muzzle, ears?

Does it shake its head as if the ears are itchy?

Has it had a history of recurrent ear infections?

Does it lick or chew or bite its feet, front or back/ dorsal or ventral surface?

Does it lick, bite, scratch or chew its axillae, belly, knees?

Does he roll on his back? chew the base or underneath the tail?

Does he scoot on his anus/perineum?

The clinician should try and determine the severity of the pruritus. This is important for two reasons. Firstly some diseases are severely pruritic (e.g canine scabies) whereas others are only mildly pruritic (e.g demodicosis, dermatophytosis). Second the level of pruritus at the initial presentation is used as a starting point to monitor the subsequent response to treatment

Assessing the level of pruritus can be particularly difficult because there is no objective scale that the clinician can use. The clinician has to rely on information provided by the client and what is observed in the consulting room. As there is no perfect way of recording the severity of pruritus, most veterinary dermatologists use one of three systems

Basic descriptors such as **mild**, **moderate** or **severe**. Although this is simple to use, the restriction to only three categories means that it is not particularly useful for assessing marginal improvements in the condition.

A **numerical score** (usually between 0 and 10). In this system clients are told that 0 is a normal dog and 10 is severe continuous scratching. The problem with this system is that owners have nothing to compare their animal to, so it is inherently inaccurate. Hence they tend to overestimate the severity of pruritus. However it does provide a starting point against which future comparisons can be made.

An **itch scale** based on more complex written descriptors (see Box) Although this allows an owner to choose a level of pruritus based on some objective criteria, it can be difficult to place some animals into a specific category. However owners are less likely to grossly over estimate the severity of pruritus with this system than with the other two.

Canine Itch Scale; Itch Includes Scratching, Biting, Licking Or Rubbing

Grade 0:	Normal dog: dog does not itch more then before the disease began.
Grade 1:	Occasional episodes of itching: small increase in itch compared with before the disease began.
Grade 2:	More frequent episodes of itching but itching stops when dog is sleeping, eating, playing, exercising or is otherwise distracted.
Grade 3:	Regular episodes of itching are seen when dog is awake. The dog occasionally wakes up because of itching, but the itching stops when the dog is eating, playing, exercising or otherwise distracted.
Grade 4:	Prolonged episodes of itching are seen when the dog is awake. The dog regularly wakes up because of itching or itches in its sleep. The itching can also be seen when the dog is eating, playing, exercising or otherwise distracted.
Grade 5:	Almost continuous itching which does not stop when the dog is distracted, even in the consulting room. The dog needs to be physically restrained from itching.

The pruritus associated with ectoparasitic skin infestations is acute in onset and may have an obvious event associated with the onset of pruritus, such as a new pet in the household, or visits to obedience or training classes, kennels or groomers. Allergic skin diseases are usually associated with a typical age of onset or seasonality (Table 17.2). There may be clinical signs other than dermatological disease such as rhinitis, sneezing and conjunctivitis in atopic dermatitis or intermittent vomiting, diarrhoea or borborygmi in adverse food reactions. Recurrent otitis externa is considered a dermatological disease and is present in the majority of dogs with adverse food reactions and atopic dermatitis. Additionally many dogs with recurrent pyotraumatic dermatitis (hot spots) have underlying allergic skin disease.

STEP 2: PERFORM A THOROUGH PHYSICAL EXAMINATION

This requires good light and magnification when necessary. I often use the little magnifier on the otoscope to look at lesions. Rolling the dog over and looking underneath the feet, as well as under the tail is important, as is rifling through the coat to see the skin over the back. You will be looking for lesions such as papules, pustules, macules, or nodules. You will also be looking for secondary lesions, such as excoriations, crusts, scale, and alopecia. Gentle otoscopy should also be performed to determine if the dog has an ear infection or whether the ear canals are merely red. During the exam, you can ask the owner which came first, the itch or the lesions. This information is useful as atopic dermatitis has often been termed "an itch that rashes" whereas a disease like scabies has primary lesions of papules which itch.

The clinical signs associated with pruritus in the dog are generally associated with self trauma such as excoriations and alopecia. Allergic skin diseases usually present primarily with erythema. The presence of papules is usually indicative of secondary bacterial involvement. Additionally pruritic papules are associated with ectoparasite infestations. Chronic pruritus whatever the aetiology is usually accompanied by hyperpigmentation and lichenification. The clinical signs associated with superficial bacterial infections include pustules, papules, patchy alopecia and epidermal collarettes. *Malassezia* infections are often found in intertriginous areas such as facial folds and feet and are usually associated with a greasy feel and odour. The distribution of the pruritus can be particularly helpful in prioritizing the differential diagnosis and is illustrated in Tables 17.2 and 17.3.

STEP 3: DEVELOP A LIST OF DIFFERENTIAL DIAGNOSES AND A PLAN BY WHICH TO SORT THEM OUT.

The differential diagnosis for the majority of cases encountered will fit into one or more of the following categories; an **ectoparasite**, an **infection** or an **allergy** (Table 17.1). The history and clinical distribution of the pruritus can help refine the differential diagnosis before diagnostic tests are initiated. The most practical and rewarding approach for all is a logical progression through a number of diagnostic and therapeutic steps keeping the client informed of the plan and expected outcome along the way.

I usually tell the clients we will develop a short term plan and a long term plan to control the itch. As a general plan, the following advice is helpful. For itch, rule out **ectoparasites**, rule out

infections, rule out **flea** and **food allergy** and then deal with what is left! Usually, what is left is atopic dermatitis, and these dogs are probably best referred for **intradermal skin testing** and **immunotherapy**. Atopic dogs will be high maintenance dogs for the rest of their lives, for both their owners and their veterinarians. The more unusual diseases associated with itch will look unusual; these are patients you will wish to biopsy for a diagnosis or refer for diagnosis and treatment recommendations.

Table 17.1. Common Causes of Pruritus in the Dog

Mechanism	**Aetiological Agent or Disease**
Ectoparasites	Sarcoptes Demodex Cheyletiella Otodectes
Infectious organisms	Bacterial infection *Malassezia* dermatitis
Allergic skin disease	Atopic dermatitis Food adverse reaction Flea bite hypersensitivity Insect hypersensitivity Contact allergy/irritant
Neoplasia	Epitheliotropic lymphoma

Table 17.2. Differentiation of allergic skin disease in the dog based on history and clinical signs

Allergic skin disease	**Seasonality**	**Age of onset**	**Distribution of clinical signs**
Flea allergy dermatitis	Seasonal	6 months	Dorsolumbar and tail base
Adverse food reaction	Non seasonal	Any time, often younger than 6 months or older dogs >8	Face, ears, perineum
Atopic dermatitis	Seasonal (pollen) Perennial (house dust mite, moulds)	Young adults 1 to 3 years	Face, ears, axillae, ventral abdomen, feet and distal limbs

Table 17.3. Distribution, zoonotic potential and preferred diagnostic procedures for common canine ectoparasites

Parasite	Distribution	Species	Sample	Zoonosis?
Sarcoptes	Elbows, hocks, ventrum, pinnal margin	Dogs	Superficial scraping	Yes
Demodex	Face, feet, trunk	Dogs	Deep skin scraping	No
Cheyletiella	Dorsolumbar	Dogs, cats, rabbits	Superficial scraping Acetate tape Flea comb	Yes
Otodectes	Ear canal, face, dorsolumbar	Dogs, cats	Superficial scraping Acetate tape	Yes

STEP 4: RULE OUT MITES AND LOOK FOR SKIN AND EAR BACTERIAL AND YEAST OVERGROWTH

The easiest and most valuable diagnostic tests to perform on the first visit are **skin scrapings** and **skin** and **ear cytology**. If you live in a flea-ridden area, then using a **flea comb** as part of your examination is also a good addition to your dermatologic toolbox.

The short term treatment plan will be to rule out scabies, to control fleas and to get rid of all microbial infections. In one month, we meet with the patient and client again to determine how much itch has been resolved by treating ectoparasites and microbial infections. Then we develop the long term plan to control residual itch. The long term diagnostic plan might be to perform elimination diet testing to rule out food allergy or perform intradermal skin testing or serum allergy testing to discover those antigens contributing to atopic dermatitis. It may include the judicious use of corticosteroids, antihistamines, and possibly cyclosporin. Diagnostic tests such as bacterial culture and sensitivity or biopsy could be part of either the short term or long term plan, depending on what the dog looks like during the first exam. Keep in mind that biopsy will not help you sort out the different types of allergic skin disease.

Skin scrapings will help us determine if mites are present. A finding of one mite or egg of *Sarcoptes* spp, *Cheyletiella* spp or *Otodectes cynotis* is diagnostic. Negative skin scrapings do not rule out the presence of mites and clinical disease with Sarcoptes, Cheyletiella and *Otodectes cynotis* mites. It is generally considered that multiple negative deep skin scrapings should reliably eliminate demodicosis from the differential list. Demodex mites can be part of the normal flora of both dog and cat skin, but it is extremely rare to find Demodex mites on skin scrapings in healthy dogs and cats. If one Demodex mite is found a case of demodicosis should be immediately suspected and further skin scrapings should be sampled.

Evaluation of cytology is a cheap, simple and rapid method of assessing for the presence of bacteria and yeast in superficial skin infections and otitis externa. For **impression smears** we rub or press a glass slide onto the surface of the lesion or exudate. This works extremely well when the skin is greasy or exudative. Do not exert too much pressure or the slide may snap. Ulcers and the surface of "pricked" papules and pustules may also be sampled in this fashion. **Sampling with a cotton bud** is useful if the skin is dry and is the method of choice for evaluating the external ear canal. Moisten with saline solution, rub on the surface of affected skin and then roll the tip onto the glass slide. Using **clear sticky tape** is also a useful technique. The type of tape used is very important because there is a marked variation in degrees of adhesiveness and transparency between brands. Press tape sticky side down repeatedly onto the lesional skin surface until it loses its adhesiveness. This means that it is covered in corneocytes. Stick one end of the tape onto a glass slide to facilitate staining.

For most routine clinical purposes, the most useful staining system is Diff Quik. This comprises a methanol fixative, a red eosin dye and a blue thiazine dye. For general staining, dip the slide into the fixative five times. Then dip the slide or tape into the red dye five times followed by the blue dye five times. At each stage the dip should last 1 second. Rinse the slide thoroughly with distilled water. If using tape then just dip the slide into the blue dye five times and omit the rinsing stage. The slide may be dried by pressing it between tissue paper. When dry adhesive tape should be examined immediately. For glass slides, the sample should be covered with a cover slip. Place a drop of immersion oil over the sample and float the cover slip on top. Adhesive tape acts as its own “cover slip” so an additional cover slip is not required.

Scan the whole slide on low power and look for areas that have stained purple. Then look at these areas under high power (x400) or oil immersion (x1000).

Ask yourselves the following questions:

- **Are the organisms yeast?**

  Malassezia pachydermatis is the most commonly implicated yeast organism, although *Candida* spp may occasionally be involved.

- **Are the organisms cocci or rods?**

  Cocci are most frequently *Staphylococcus intermedius*, although *Streptococcal* spp may be found in some patients. Rod-shaped organisms are found most often in the ear canal and are usually *Pseudomonas aeruginosa* and *Proteus mirabilis.*

- **Number of organisms**

  The number of organisms is important. Most dermatologists consider that one or more yeast per high power field is relevant, whereas cocci should be seen in high numbers.

- **Type of inflammatory cell (neutrophils, eosinophils, lymphocytes, plasma cells, macrophages, giant cells); degenerative vs non degenerative; presence of phagocytosis.**

  Inflammatory cells with intracellular organisms are diagnostic for infection; eosinophils are typical of parasitic or allergic skin disease

STEP 5: USING A THERAPEUTIC TRIAL

Therapeutic trials are valuable and are employed as diagnostic tools in dermatology. Common scenarios are as follows:

A. **Failure to find scabies mites in the dog with a suspected infestation does not rule out a diagnosis of sarcoptic mange**

   Trial therapy with a scabicidal agent should be undertaken over a six week period. A single dose of ivermectin is insufficient to rule out this parasite, and in our dermatology clinic we recommend the application of **selamectin (Revolution ® Pfizer) at 6mg/kg for three treatments at two week intervals.**

B. **Failure to find pustules does not rule out a superficial bacterial folliculitis or superficial bacterial pyoderma.**

   Bacterial overgrowth and bacterial infections take many clinical forms, depending on the stage of the disease and the skin structure affected. Thus they can present as pustules, papules, epidermal collarettes, scale, greasy erythemic patches or patchy alopecia. Combined therapy with systemic and topical antibacterial therapy for three to four weeks is recommended.

C. Failure to find fleas does not rule out a diagnosis of flea allergy dermatitis in the dog with seasonal dorsolumbar pruritus.

Under these circumstances confirmation of the diagnosis is made by resolution of the symptoms with a flea therapeutic trial. As a general rule the response (or lack thereof) of a therapeutic trial is assessed at Day 28. A flea therapeutic trial in the dog in our dermatology clinic involves giving **oral nitenpyram (Capstar ® Novartis) 1mg/kg PO q 24hrs for 30 days.**

Interpretation of the Flea Therapeutic trial

- A good response (>80%) is consistent with FAD
- A moderate response (30 to 80%) warrants continuing for a further 14 to 21 days
- If there is no further response (still 30 to 80% at Day 42) there may be concurrent disease e.g. FAD and atopy or an adverse food reaction
- A poor response (< 30%) suggests FAD is unlikely

STEP 6: FURTHER INVESTIGATION: DOES THIS DOG HAVE A FOOD ALLERGY?

In most cases, it is not appropriate to initiate an “allergy work-up” on the first visit. Further investigation is generally indicated when secondary bacterial or yeast infection or otitis externa becomes recurrent or there is a persistence of pruritus despite instituting flea control and appropriate antimicrobial therapy.

In all cases of persistent non seasonal pruritus, however, after ruling out mites and infection, we will perform an **elimination diet trial**. In some cases these dogs will have a history of seasonal pruritus, implicating environmental allergens in their disease. However, if even a mild pruritus persists year round then an adverse reaction to food (AFR) cannot be ruled out as a component of the problem.

No sex predilection has been reported for AFR in dogs. Some breeds such as Labradors, German Shepherds and West Highland White terriers and Spaniels may be overrepresented While the age at onset of pruritus has been reported as variable, namely from 2 months to 14 years, approximately 50% of canine AFR patients have an age of onset of pruritus of younger than one year. Clearly while AFR may occur at any time in a dog's life, it should always be considered as a differential diagnosis of pruritus in young dogs.

AFR are usually non seasonal and often occur suddenly after months or years of consuming the diet containing the inciting foodstuff.

The most common clinical sign of AFR in dogs is a non seasonal pruritus. The response of pruritus after administration of corticosteroids is controversial. It has been considered, that in contrast to atopy, AFR mostly react poorly on systemic treatment with corticosteroids. However studies report patients with a total response to pruritus following treatment with corticosteroids.

The pruritus can be generalised or limited to the face, ears, feet, and pinna, and axillae, inguinal or perineal region. Anal pruritus has been reported in dogs with colitis and in human patients with food allergy and pruritus in the perineal region. Some recent studies suggest that AFR should be considered as an important differential diagnosis in dogs with perineal and anal pruritus.

Unilateral or bilateral otitis externa is observed in up to 80% of dogs with AFR and up to 25% of dogs with AFR in the **absence of any other clinical signs**. Otitis can be purely inflammatory, where macroscopic and otoscopic examination reveals erythema of the medial aspect of the pinnae extending into the vertical external ear canal in the absence of any otic exudate. Recurrent secondary bacterial and *Malassezia* otitis externa based on clinical signs and cytology is a common complication of otic inflammation in canine AFR. This suggests that AFR are an important cause of recurrent unilateral or bilateral otitis externa in the absence of any other clinical signs.

The most common primary skin lesion reported in dogs with AFR are papules and erythema. Pustules, plaques, angioedema and urticaria have also been reported. Common secondary lesions include excorations, lichenification, alopecia, scaling, crusting, hyperpigmentation and moist erosions appearing as pyotraumatic dermatitis.

Superficial bacterial pyoderma and *Malassezia* dermatitis are a common complicating factor in canine AFR and in some dogs, pyoderma (superficial or deep) can be the only clinical sign of an AFR; these dogs are clinically normal (non-pruritic) while receiving antibiotics. It is therefore important to diagnose and treat secondary infections in dogs with AFR because the resulting pruritus may confound the clinician's ability to diagnose the underlying allergy.

Gastrointestinal tract symptoms including vomiting, diarrhea, flatulence, borborygmi and an increase in faecal mucous, faecal blood, tenesmus and an increase in the frequency of defaecation occur in some dogs with cutaneous clinical signs of AFR. The reported frequency of gastrointestinal tract symptoms in dogs is variable but in more recent studies where owners were questioned specifically about gastrointestinal symptoms, gastrointestinal signs were observed in 60% to 65% of dogs with AFR. Gastrointestinal problems may not be reported by owners during a dermatology consultation and are often accepted as unrelated problems which may explain the lower percentages and the apparent absence of gastrointestinal signs in other studies. Although gastrointestinal signs are significantly more common, however in dogs with the condition than in those without it, the lack of them cannot rule out the condition as a possible differential diagnosis.

In many cases, dogs with AFR have clinical signs that are similar to those described for canine atopic dermatitis and only concurrent gastrointestinal problems and marked perianal pruritus were more frequent in dogs with AFR than in dogs with atopy. It is therefore important to question an owner carefully about the presence of anal pruritus and subtle gastrointestinal symptoms as this is one clinical feature that may assist in distinguishing AFR from atopy in a clinical setting.

Neurologic signs such as malaise and seizures rarely have been reported. The author feels that malaise may be under-reported, as an increase in energy level ('acting like a puppy, feeling better') is often noted upon feeding the dog a diet without the offending allergen; this may occur before cessation of pruritus. While behavioural abnormalities are well recognized in children with food hypersensitivities they are not well documented in the veterinary literature. It may be important to question an owner carefully about the presence of subtle behavioural changes as this is another clinical feature that may assist in distinguishing AFR from atopy in a clinical setting.

In dogs, diagnosed with AFR, up to 50% are reported to have concurrent cutaneous hypersensitivities including atopy and flea-bite hypersensitivity. This is important from a clinical perspective as dogs with concurrent atopic dermatitis may only demonstrate a partial reduction in pruritus while receiving an elimination test diet.

Definitive diagnosis of an AFR relies on observing improvement of clinical signs when the animal is fed a novel protein diet followed by demonstrating recurrence of clinical signs when oral provocation with a previously fed foodstuff is performed. The diet should be fed for a minimum of 6 weeks, although some cases may continue to improve for up to 8 to 10 weeks. The primary objective is to select a food combination that has minimal or no history of previous exposure. Most dogs have eaten commercial diets containing a variety of different ingredients from protein and carbohydrate sources. Selecting items that are unique to the diet can be challenging. Studies have suggested that commercial diets are not as accurate in diagnosing AFR as home prepared diets. **It is recommended that a home prepared elimination diet should be considered as the gold standard for diagnostic purposes.**

There are some limitations associated with a home prepared diet using a unique or novel protein source. Firstly some protein sources are expensive for the owner to purchase or may only be found in limited quantities. Secondly home cooked diets entail some work by the owner that can be tedious. Finally home prepared diets are not usually complete and nutritionally balanced. The most common nutritional inadequacy is a deficiency of calcium and too low Ca:P ratio, which is an inevitable consequence of an unsupplemented meat based diet. Other common deficiencies include vitamin B12, E, D and A; copper, manganese and iodine. Common high in protein and low in calcium. Non dietary sources of calcium, vitamins and essential fatty acids should be added to the diet. For clinically healthy dogs and cats, the short duration of the feeding trial should not lead to major nutritional deficiencies, however in rapidly growing large breed dogs and dogs with concurrent metabolic illness the diet should be supplemented. A useful website for obtaining balanced diets for an individual animal that requires a long term home prepared diet is www.Balanceit.com

Several commercial diets have been formulated for the diagnosis and management of food allergic dogs and cats. Novel protein sources, such as egg, fish, duck and rabbit and others are available from commercial producers. Potato has been used in combination with various protein sources. There are also many commercial diets available that contain fish (e.g catfish, whitefish, salmon). There is limited scientific evidence which shows that some dogs and cats will improve on a home cooked diet but experience a recurrence of signs when fed a commercially available diet containing the same ingredients.

Table 17.4. Novel Protein diets available in Australia

Diet	Constituents
Hill's Prescription Diet i/d canned canine	turkey, egg, rice, ground whole grain corn, pork liver, soy fibre
Hill's Prescription Diet i/d dry canine	ground whole grain corn, rice, egg, chicken meal, pork fat, soybean oil, cellulose
Hill's Prescription Diet d/d egg and rice formula dry canine	brewers rice, egg product, pork fat, soybean oil, cellulose, fish oil
Hill's Prescription diet i/d dry feline	chicken meal, rice, corn gluten meal, ground whole grain corn, pork fat cellulose, dried chicken, chicken liver flavour
Hill's Prescription Diet z/d low allergen feline	hydrolysed chicken, rice and vegetable oil
Hill's Prescription Diet i/d canned feline	pork liver, pork by-products, chicken, wheat flour, chicken fat, corn starch, rice, dried chicken liver flavour
Eukanuba FP Response dry	herring, catfish, potato, animal fat, fish digest, beet pulp
Eukanuba FP Response canned	herring, catfish, potato, fish digest, beet pulp

There are several hydrolysed protein based diets commercially available in Australia (Table 17.5).

During hydrolysis, protein sources, including chicken, poultry liver, soy and casein are enzymatically broken down to polypeptides, changing and reducing the allergenic properties of the molecules. The primary aim of a hydrolysed protein diet is to sufficiently disrupt the proteins within the diet as to remove any existing allergens and prevent recognition by a patient sensitized to the intact protein. Initial selection of a commercial hydrolysed protein diet for a patient should probably be based upon the protein source. None of the currently available diets are sufficiently hydrolysed to guarantee the complete absence of any allergens. Therefore it is prudent to select a diet that does not contain a protein source that the patient is known or suspected to be sensitized to. Secondary consideration should be given to the sources of carbohydrate and lipid as sources of potential protein allergens and as sources of carbohydrate or lipid antigens.

The limitation to the use of hydrolysate diets, however as elimination test diets is the lack of reports of their efficacy in proven chicken, soy or casein-allergic dogs. In one study using the Royal Canin soy hydrolysate diet, 2 dogs that did not improve when fed the soy and chicken based hydrolysate, did improve when fed either a home prepared soy-based diet or a commercial rabbit and rice diet (Biorge 2004). These findings suggest either a sensitization to the chicken or other protein fraction within the hydrolysate diet or the creation of novel dietary antigens as the result of the food processing. When the Nestle-Purina HA soy hydrolysate diet was fed to a colony of soy and/or corn allergic Maltese-beagle dogs, 3 of 14 dogs relapsed with cutaneous and gastrointestinal signs but it is not uncertain which fraction the dogs were reacting to (Jackson 2004).

This study demonstrated for the first time, that a commercially available hydrolysate diet can be fed to the majority of dogs sensitized to the intact protein source without eliciting clinical signs. However it also indicated that a significant proportion (21%) of dogs sensitized to the intact compounds will still react adversely to the hydrolysed diet. This reemphasizes the limitations of the currently available hydrolysed protein diets. For maximum confidence in performing an elimination diet trial, it is still important even when using a hydrolysed protein diet to obtain an accurate dietary history and to choose a diet that contains ingredients the patient is unlikely to be sensitized to.

Table 17.5. Hydrolysed diets available in Australia

Diet	Constituents
Hill’s Prescription Diet z/d ultra canine	hydrolysed chicken, maize starch cellulose and soybean oil
Hill’s Prescription Diet z/d canine low allergen	hydrolysed chicken, potato, potato starch, cellulose and soybean oil
Hill’s Prescription diet z/d ultra canine and feline canned	hydrolysed chicken, corn starch and soybean oil
Hill’s Prescription Diet z/d low allergen feline	hydrolysed chicken, rice and vegetable oil
Royal Canin Hypoallergenic DR21 canine	hydrolysed soya protein isolate and hydrolysed poultry liver, rice, beet pulp, poultry fat, borage oil
Royal Canin Hypoallergenic DR25 feline	hydrolysed soya protein isolate and hydrolysed poultry liver, rice, beet pulp, animal fats, vegetable oils, fish oil
Nestle-Purina HA (NZ only)	hydrolysed soy, corn starch, cellulose, vegetable gums, coconut oil, canola oil, corn oil

Interpretation of the Response on the Diet

In patients with dermatologic signs, pruritus is the most important symptom that is evaluated during the elimination diet. The interpretation of a patients response to the elimination diet can be hampered by a partial or coincidental response, the influence of secondary bacterial or yeast infection or a treatment that has been used simultaneously to manage pruritus.

A **partial response** occurs when concurrent allergies are present or in atopic patients that go through a fluctuation in severity. This can be responsible for a false diagnosis of AFR. To prevent this problem, it is necessary to repeat the food trial several times, until both the owner and the clinician are fully convinced that the diet is the determining factor in preventing the symptoms.

Secondary bacterial and yeast infections occur frequently in dogs with AFR and treatment is often prescribed simultaneously with the start of an elimination diet. It is important to maintain the treatment during challenge testing, because otherwise infections can reappear and wrongly suggest that the patient relapsed on the food. Related problems are the cases of recurrent pyoderma following AFR in dogs. Pruritus in these patients is only caused by the bacterial lesions and completely resolves after treatment with antibiotics. Diagnosis of this non pruritic form of AFR with secondary pruritic pyoderma is very difficult, especially if the period between the relapses is significant. In this situation, the clinician has to determine if the elimination diet prevents the relapse of the pyoderma but this can take a substantial period of time. It can be difficult to maintain the cooperation and the compliance of the owner in these circumstances.

Treatment with corticosteroids is only advised when absolutely necessary in dogs and cats with intense and severe pruritus and then should only be prescribed for a short period (1 to 3 weeks).

Finally, if there is no improvement after the elimination diet, then the owner must be informed that the pruritus is due to another cause or an allergen in the elimination diet.

Confirming Food Allergy

A diagnosis of AFR is confirmed by demonstrating that the clinical signs recur when previously fed foodstuffs are re-introduced. This is achieved by feeding a test meal of the dog or cat’s previous diet including treats for 10 to 14 days. Some owners will refuse to a challenge with the former food after reduction in clinical signs, but it is important to underline the importance of the challenge test, because a significant placebo affect can occur in 20% of cases. This means that continuing the elimination diet will be useless in some patients.

When the clinical signs will reappear is a subject of debate. Most dermatologists agree that the majority of dogs that will relapse within 24 to 72 hours although there are reports of reactions taking up to 21 days· Once a documented reaction is noted the animal should be placed back on the elimination test diet.

Identification of Specific Food Allergies

A sequential rechallenge involves feeding each of the major food items that were contained in the original diet reported to cause AFR in dogs (beef, dairy, wheat, soy, chicken, lamb, eggs) by adding one pure food ingredient to the restrictive diet to determine which individual allergen or allergens is incriminated. Between 35% to 60% of dogs are reported to be intolerant to more than one foodstuff underscoring the need for challenge with multiple food sources.

Clinical Management

On the basis of information obtained from the sequential rechallenge, a commercial food that does not contain the offending substance can usually be selected. Canned diets require fewer preservatives than dry foods and may therefore be better tolerated. About 20% of food hypersensitive dogs, however, **cannot consume any commercial diet** and must be maintained on a home prepared diet. These animals must be maintained on a balanced home-cooked diet with additive free vitamin and mineral supplements.

Table 17.6. Diets suitable for maintenance available in Australia

Diet	**Constituents**
Hill's Science Diet Sensitive Skin	Brewers rice, ground whole grain corn, corn gluten meal, pork meal, dried egg product, soybean oil, flaxseed, animal fat, chicken liver flavour, fish oil EPA and DHA 1.37% linoleic acid 4.67%
Hill's Prescription Diet z/d canine low allergen dry	hydrolysed chicken, potato, potato starch, cellulose and soybean oil EPA and DHA 0.38% linoleic acid 0.99%
Hill's Prescription diet z/d ultra canine and feline canned	hydrolysed chicken, corn starch and soybean oil EPA and DHA 0.12% linoleic acid 1.07%
Hill's Prescription Diet z/d low allergen feline dry	hydrolysed chicken, rice and vegetable oil EPA and DHA 0.61% linoleic acid 5.3%
Royal Canin Sensitivity Control SC 24 canine dry	fish (blue whiting), tapioca, animal fats, poultry liver hydrolysate, soya oil, fish oil, tyrosine, biotin, niacin, pantothenic acid EPA and DHA 0.7% linoleic acid 1.6%
Royal Canin Sensitivity Control SC 31 feline dry	fish (blue whiting), rice, animal fats, poultry liver hydrolysate, soya oil, fish oil, tyrosine, biotin, niacin, pantothenic acid EPA and DHA 0.9% linoleic acid 2.3%
Royal Canin Sensitivity Control SC 24 canine canned	chicken meat, chicken liver, rice, fish oil, sunflower oil; biotin, niacin, pantothenic acid EPA and DHA 0.93% linoleic acid 5.0%
Royal Canin Skin Support SS 23 canine dry	fish, rice, animal fat, fish oil, soy and borage oil, turmeric, tyrosine; biotin, niacin, pantothenic acid; EPA and DHA 1.84% linoleic acid 2.1%
Royal Canin Hypoallergenic DR21 canine	hydrolysed soya protein isolate and hydrolysed poultry liver, rice, beet pulp, poultry fat, borage oil, biotin, niacin, pantothenic acid EPA and DHA 0.35% linoleic acid 4.1%
Royal Canin Hypoallergenic DR25 feline	hydrolysed soya protein isolate and hydrolysed poultry liver, rice, beet pulp, animal fats, vegetable oils, fish oil EPA and DHA 0.32% linoleic acid 4.5%

STEP 7: FURTHER INVESTIGATION: DOES THIS DOG HAVE A ATOPIC DERMATITIS?

The diagnosis of atopic dermatitis is based on typical history and clinical presentation (Table 17.2) and most importantly by exclusion of other pruritic skin diseases. In mild cases with seasonal disease, symptomatic therapy for the months the individual dog is affected may be sufficient. In more severe cases with perennial disease, intradermal allergy testing and/or serum allergy testing with view to initiating allergen specific immunotherapy may be indicated.

Atopic dermatitis is the second most frequent allergy in dogs. Strong breed predilections, familiar involvement, and limited breeding trials have demonstrated that canine atopy is genetically programmed with Golden Retrievers, Labradors, Terriers, Dalmatians, and Shar-peis among the predisposed breeds. In Australia, German Shepherds, Rottweilers, Bull Terriers, West Highland White Terriers and Boxers are predisposed.

Atopic dermatitis may be seasonal or year round. Dogs most commonly start showing signs between one to seven years of age. The average age of affected dogs is 12 to 18 months with 95% of the dogs first showing clinical signs at less than 5 years of age. Exotic breeds, such as the Akita, Shar-pei and Chow Chow, may show signs as young as six months. Initially, the season may be quite short, but as (presumably) the dog becomes allergic to more allergens, perennial pruritus frequently results.

Lesions in dogs are generally found on the feet, ears, axilla, and face, with conjunctivitis present more frequently than is commonly reported. Recurrent otitis externa is common. Pruritus, erythema, alopecia and hyperpigmentation are the most frequent clinical signs

Atopic dogs are prone to secondary infections with *Staphylococcus intermedius* and *Malassezia pachydermatis*. Thus, clinical signs of superficial pyoderma (epidermal collarettes, papules), or yeast infection (waxy brown exudate on skin or proximal claws, erythema interdigitally or under tail) are common.

Atopic dermatitis is diagnosed by history, physical examination, and ruling out other causes of pruritus, especially food allergy, ectoparasites, etc. Atopic dermatitis is then definitively diagnosed by intradermal allergy testing (IDAT) or serologic tests (ELISA) looking for allergen-specific IgE. The comparable efficacy of intradermal testing versus *in vitro* serologic testing in atopic individuals remains controversial. Both tests are prone to false positive and false negative results. They should not be used to diagnose atopy, but can be used to better define allergens for avoidance or inclusion in immunotherapy vaccines.

There is only partial correlation between serum tests and intradermal testing. It is important to note that intradermal testing and *in vitro* serology are measuring different things (fixed tissue IgE vs circulating antigen specific IgE) and that serum IgE does not necessarily correlate with cutaneous IgE levels and skin reactivity. 10 to 15% of clinically atopic dogs have negative intradermal and *in vitro* serologic tests that cannot be explained by false negative reactions. Interestingly, the success of immunotherapy based on data supplied by each is similar. There is some data to suggest that the utilisation of both tests together in screening for offending allergens may improve overall success of immunotherapy.

SUMMARY: DIAGNOSTIC PLAN FOR INVESTIGATING CANINE PRURITUS

Table 17.7. Diagnostic plan for investigating canine pruritus

1. Rule out ectoparasitism • Microscopic examination of skin scrapings and acetate tape • Ear swab for Otodectes and Demodex mites • Acaricidal trial
2. Evaluate the role of bacterial / *Malassezia* overgrowth / infection • Skin surface and ear cytology • Trial therapy with antibacterial agents
3. Investigate allergic skin diseases • Non seasonal pruritus • Feed a strict elimination diet for 6 to 10 weeks • Consider serological or intradermal allergy testing if the client is willing to administer allergen specific immunotherapy
4. If there is a poor response to therapy or no diagnosis • Perform a skin biopsy

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Chapter 18

Atopic Dermatitis and Pruritus: Pathophysiology and Principles of Management

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PATHOGENESIS AND PATHOPHYSIOLOGY: WHO CARES??

Understanding the pathogenesis of a disease is about understanding the how the disease occurs (it's evolution). Understanding the pathophysiology of a disease is about understanding how the disease disrupts the normal physiological functions of the body to cause the symptom that we see in our patients. Imagine how successful we would be treating diabetes if with did not know understand the role of insulin. Understanding pathogenesis and pathophysiology allows us to make rational and specific choices for treatment AND if we understand the disease we are treating we have a far greater chance of being able to explain the disease to our clients. Client's ability to understand their pet's disease has a major impact on their compliance. Without knowledge of pathophysiology we would try and treat every coughing dog the same way regardless of the underlying disease and pathological mechanisms causing the cough. This would be a ridiculous situation and would lead to poor outcomes. It is equally unrealistic to expect that a single treatment will be effective in all cases of pruritus. Understanding the basic mechanisms leading to pruritus and how that may vary from disease to disease can be very helpful in our therapeutic choices.

With the exception of flea-bite hypersensitivity, atopic dermatitis is the most common skin disease of dogs. It is so common that all of you that work in small animal practice will see itchy dogs almost daily. Of those dogs with relapsing itchy skin, over half will be atopic. Atopic dermatitis is a life-long disease that requires COMPLIANT management to allow the patient to have a high quality life. It is a complex disease with multiple mechanisms of itch generation. THERE IS NO SINGLE TREATMENT THAT WILL BE EFFECTIVE IN ALL ATOPIC DOGS. In this session I hope to increase your understanding of the pathogenesis and pathophysiology of pruritus and atopic dermatitis in the dog. I hope that this will allow you to better explain this disease to your clients and to assist in better treatment choices and better outcomes for your atopic patients. Who cares about pathogenesis and pathophysiology? You do!!

PATHOGENESIS OF PRURITUS

Pruritus, What Is It?

Pruritus is defined as a sensation that elicits the desire to scratch or induces scratching. It is commonly referred to as “itch”. The most objective measure of pruritus is observed scratching however pruritic behaviour may also involve pinching, slapping, rubbing, licking, biting, rolling, barbering and feather plucking depending on the species involved.

Types Of Pruritus

1. Pruritoceptive itch is an itch originating from the skin eg the dominant form of itch in atopic dermatitis
2. Neuropathic itch is an itch arising from neuroanatomic dysfunction eg nerve entrapment injuries.
3. Neurogenic itch is an itch arising from neurochemical action eg opioids. It is generally associated with systemic disease eg liver disease but it may also be the mechanism of itch associated with dry skin in atopic dermatitis
4. Psychogenic itch is a delusional state.

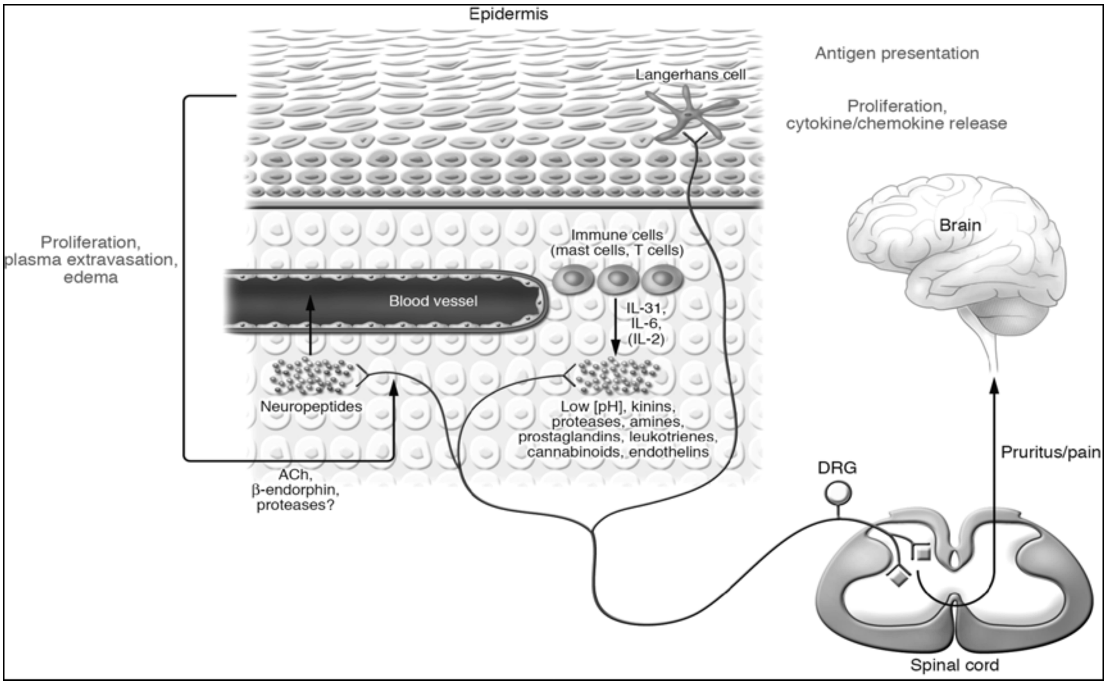

Image 18.1. Neuroanatomy of itch (from Paus et al 2006)

Peripheral Processing

The primary afferent neurones (sensory neurones) are located in the dorsal root ganglia of spinal nerves or the sensory ganglia of cranial nerves. Axons of neurones that conduct itch are unmyelinated C fibres that terminate at the dermoepidermal junction (DEJ) or penetrate into the epidermis as free nerve endings. Substance P (SP), neurokinin A and calcitonin gene related peptide (CGRP) are the main transmitters. C fibres associated with conduction of histaminergic itch (pruriceptors) are slow velocity fibres that have large innervation territories compared to polymodal C fibres. They comprise about 5% of afferent C fibres in the skin. They are responsive to pruritogenic stimuli and thermal stimuli but not mechanical. Other classes of primary afferents exist that are involved with histamine independent generation of pruritus. Diversity of afferent fibres probably explains some the variations in perceived itch quality. This may be contribute to variation in itch behaviours seen in the patient.

Once C fibres are activated there is release of transmitters into the tissue (neurogenic inflammation) and orthodromic transmission is processed along the peripheral nerves to the spinal ganglia. Nocioceptor afferents terminate in the superficial area of the dorsal horn and “itch” specific neurones have been identified in the cat in the dorsal horn lamina 1 spinothalamic tract.

Chronic triggering of itch nocioceptors may results in release of nerve growth factors and increased “itch” nociceptors density in affected areas.

Heat activated and cold activated vanilloid and cold-menthol sensitive receptors TRPs (transient receptor potential) can modulate peripheral itch processing. They are inducible receptors belonging to a family of excitatory ion channels. They can be activated by heat and cold and may explain why itch perception is increased by warm skin and decreased by cold. They can also be upregulated by inflammation (eicosanoids). There are a variety of vanilloid receptors expressed on mast cells that allow for thermal and mechanical degranulation. Maybe upregulation of vanilloid receptors in atopic dogs explains their sensitivity to post clipping pruritus??

Itch may be under tonic inhibitory control of pain-related signals. In fact the inhibition of itch achieved by scratching may directly relate to the generation of pain signals from the skin. The bigger the itch the greater the need to excoriate (cause pain signal) to shut down the itch.

Spinal Processing

There are itch specific fibres that project up the spine (spinothalamic tract) to the ventral medial nucleus and the medial dorsal nucleus of the thalamus. Itch processing at the spinal level may also be under tonic negative control. This can be abolished (eg morphine) and result in pruritus triggered at a spinal level.

Central Processing

Several pathways from the thalamus to the cortex have been distinguished. Neurones from the ventral medial nucleus terminate in the 3a region of the sensorimotor cortex whereas neurones from the medial dorsal nucleus terminate in the anterior cingulate cortex. Involvement of the motor cortex explains the urge to scratch. Involvement of the anterior cingulate cortex may explain the emotional influences on “itch”. The animal’s temperament may alter the perception and response to the itch. Central imaging studies in histamine induced scratching also suggest involvement of the supplemental motor area, premotor area, prefrontal cortex, orbiofrontal cortex, cerebellum and periaqueductal gray. These centres are also activated in pain. Involvement of the frontal lobe cortices may explain the compulsive nature of itching in some patients.

What Makes Us Scratch?

Pruritus originating from skin disease is what we are most familiar with. Ultimately the severity of pruritogenic itch is dependent on mast cell density, innervation territories, the concentration of liberated mediators, the rate of degradation versus liberation and the interaction between mediators, transmitters and neurones together with spinal and central processing of those signals. Liberation and degradation of mediators as well as tachyphylaxis to mediators and up-regulation and inhibition of spinal and central pathways is a dynamic event. Put simply it is a complex immuno-neurological event.

Mediators of Pruritoceptive Itch

Acetylcholine (ACh)

Acteylcholine causes itch in atopics and burning sensation in non-atopics. Reaction to acetylcholine may explain itching with sweating in atopics. Itching induced by ACh is thought to be mediated by muscarinic AChR. It is released by keratinocytes during cutaneous inflammation and T-lymphocytes .

Amines

Histamine

Released from degranulating mast cells and basophils. Histamine can also be released from macrophages and lymphocytes in smaller levels.

Histamine acts as a neurotransmitter in neurones via H1 receptor interaction. H3 receptors have been identified on peripheral endings of SP positive fibres and may play a role in modulating itch. There is an inverse relationship between H1 and H3 receptor activation and itch. H3 agonists may reduce H1 mediated .H4 receptor activation also increases itch.

Serotonin

Released from mast cells. Serotonin acts as a neurotransmitter and both peripheral and central receptors may be involved. Itch is less potent than histamine but is enhanced by prostaglandins. Cutaneous itching associated with serotonin may be mediated by 5HT2 receptors. Serotonin also has a central role in itch perception and may play a role in neurogenic itching of uremic patients in people.

Cytokines

Interleukin 2 (T-cells) is a potent inducer of itch.

IL 31 (T-cells) has been shown to induce pruritus in mice and is over-represented in lesional skin of atopic people. IL 31 is a T cell cytokine with mRNA being over-expressed in CLA+ memory T-cells. It has been identified in the thymus of atopic dogs but not yet identified in skin.

Eicosanoids

Eicosanoids are liberated from infiltrating leucocytes and mast cells. They activate both TRPV1 and TRPV4 receptors (have endovanilloid functions). Prostaglandins reduce the threshold for pruritus induced by other mediators The mechanism of this may involve their endovanilloid action. Leukotriene B4 is pruritogenic in the mouse. PAF stimulates itch that is histamine mediated. Eicosanoids also stimulate production of Th-2 attracting chemokines and promote Th-2 T-cell recruitment during inflammation.

Neuropeptides

Substance p

SP reactive nerve fibres are found in the skin and are particularly numerous around blood vessels and sweat glands. C fibre activation results in SP release and neurogenic flare. This requires intact axons (is an axon reflex) and includes release of eicosanoid mediators of inflammation AND histamine release from dermal mast cells AND has direct pruritogenic effects. In people the severity of the reaction in decreased by stress and increasing age and increased at night.

Calcitonin gene related peptide

Tends to co-localise with SP in the skin. It causes vascular changes (erythema) but is NOT mediated via histamine or abolished by blocking axonal transmission. It is a major neurotransmitter along with SP in peripheral and central neurones.

Vasoactive intestinal peptide (VIP):

VIP and acetylcholine co-localise in autonomic nerve fibres. VIP is increased in atopic skin.

Endothelin acts as a neurotransmitter on C fibres within the skin. Mast cell degranulation up-regulates endothelial endothelin release and modulates degradation of endothelin via neutral proteases

Neurotensin

Neurotransmitter that may interact with dopamine and opioid receptors centrally.

Neurotrophins

Nerve growth factor is involved in control of skin sensation and may play role in pruritus in atopic dermatitis. It is pruritogenic when injected into the skin. Increased neurotrophin production in AD reduces itch threshold, up-regulates vanilloid receptors and up-regulates SP production.

Opioids

υ agonists induce pruritus. It is likely that tonic inhibition of itch involves pain pathways. Analgesia via υ agonists may abolish this tonic inhibition and lead to central perception of pruritus. Central υ opioid receptors are up-regulated in AD. κ agonists (spinal level) inhibit pruritus.

β endorphins from keratinocytes and enkephalins increase histamine responses in the skin without increasing histamine levels or inducing eicosanoid release. They can also affect central perception of itch via interaction with opioid receptors and possibly serotonin.

Proteases and Kinins

Chymase

Skin mast cells release the neutral protease chymase along with histamine during degranulation. Chymase greatly augments histamine-induced wheal formation in Ragweed sensitized dogs and this is abolished by blocking H-1 receptors. Chymase augments histamine mediated itching presumable by increasing histamines affinity with H1 receptors.

Tryptase

Tryptase induces itch via activation of proteinase-activated receptor 2 (PAR2) on sensory neurones and induces neuropeptide release. Both chymase and tryptase are released together with histamine when mast cells degranulate PARs play a key role in pruritus during neurogenic inflammation AND serine protease driven itch associated with dry skin PAR2 receptors may also be activated by EXOGENOUS proteases eg microbial and environmental to induce itch. Tryptase released from degranulated mast cells activates PAR*2* at the plasma membrane of sensory nerve endings. Activation of PAR*2* by tryptase, trypsins, kallikreins stimulates the release of calcitonin gene–related peptide (CGRP) and tachykinins, e.g., SP, from sensory nerve endings. CGRP interacts with the CGRP1 receptor to induce arteriolar dilation and hyperaemia. SP may stimulate degranulation of mast cells, providing a positive-feedback mechanism. Tryptase degrades CGRP and terminates its effects. CGRP inhibits SP degradation by neutral endopeptidase and also enhances SP release, thereby amplifying its effects. At the spinal cord level, PAR*2*-induced intracellular Ca2+ mobilization leads to release of CGRP (and SP) from central nerve endings, thereby activating CGRP receptor (CGRPR) and NK1R to transmit itch responses to the central nervous system. PAR 2 activation (similar to TRPV1) may be involved with the lowering of the pruritic threshold in chronic skin inflammation. PAR2 expression in the spinal and central neurons implies PARs may play a role in spinal and central mediation of itch as well.

Other Proteases

From keratinocytes and protease IV from endothelial cells and/or probably exogenous proteinases (bacteria, house dust mite, pollens) also activate PARs.

Kallikrein: PAR2 activation.

Bradykinin: Endovanilloid activity

Why Does Scratching Modulate Itch?

When a large area of skin is scratched or rubbed there is activation of touch and pressure conducting myelinated A fibres resulting in down regulation of itch processing at the level of the substantia gelatinosa. The dorsal horn also receives inhibitory signals from the mid-brain periaqueductal region. Rubbing therefore can modulate itch (and pain). The scratch reflex is a more common response to itch to counteract the itch by slightly painful stimuli. This itch reduction is based on a spinal antagonism between pain- and itch-processing neurons

Take Home Message re Pruritus

Pruritus is multifactorial in origin and a complex interaction between mediators, and neurotransmitters with peripheral, spinal and central processing. Not surprisingly the best treatment for pruritus is diagnosis and removal of the trigger. Relevant to our next discussion on atopic dermatitis is that dry skin, environmental and microbial proteases are very important in the generation of atopic itch. That intervention is often needed to modulate the itch and prevent self-trauma AND that in neglected disease it may be the itch that gets worse not the disease getting worse. This means that the perception and transmission of itch is INCREASED in chronic disease.

PATHOPHYSIOLOGY OF CANINE ATOPIC DERMATITIS(CAD)

Atopic dermatitis has been defined by an international task force on canine atopic dermatitis (CAD) as "a genetically-predisposed inflammatory and

Pruritic allergic skin disease with characteristic clinical features that is associated most commonly with IgE antibodies to environmental allergens". This definition will need ongoing modification, as we understand more about the pathogenesis of this complex disease.

Genetics and IgE

Our current understanding of the pathogenesis of atopic disease indicates both genetic and environmental factors affect expression. A role for genetics is easily accepted given the over-expression of CAD in some breeds that we see in clinical practice. The nature of this genetic influence though is unknown. In a study comparing Canine Leucocyte Antigen haplotypes in normal and intradermal skin test positive dogs undergoing immunotherapy, the combination of DLA-3, R15 had a positive correlation with clinical CAD but not with serum IgE levels. High IgE production is dominantly inherited but a correlation between genetically programmed high IgE production and the later development of clinical CAD has not been demonstrated

It clearly takes more than the presence of allergen specific IgE to cause CAD. Intuitively it makes sense that clinical disease requires receptor bound allergen specific IgE in the skin, the allergen must be environmentally relevant and must gain access to the host.

Genetics and Epidermal Barrier Function

The skin is an amazing organ. One of it's major jobs in life is to protect us from our environment. It does this by forming barrier layer as the outermost layer of the skin (the cornified layer or stratum corneum). This barrier layer is made up of dead (cornified) skin cells, glued together at the edges (corneodesmosomes) and embedded is special lipids (ceramides or sphingosines, triglycerides, free fatty acids). Ceramides are the most important lipid component for the lamellar (layered) arrangement of the barrier layer and consequently as a barrier function as they allow stretching and bending. The polyunsaturated fatty acids, e.g. linoleic acid (omega 6 oils), are incorporated into the ceramides.

Allergens triggering IgE responses are hydrophilic. A functional epidermal barrier effectively minimises the penetration of both hydrophilic and hydrophobic molecules through the stratum corneum. Poor barrier function increases the size of peptides that can be absorbed through the skin. Percutaneous penetration of allergens through barrier-disrupted skin promotes a Th-2 response (characteristic of atopic dermatitis) and IL-4 inducible IgE is correlated to the degree of disruption. This suggests that barrier dysfunction may play a role in sensitisation as well as the elicitation phase of atopic dermatitis.

Maybe our focus on the genetic ability to make lots of IgE as a cause for CAD is misplaced and we need to look more at epidermal barrier function/dysfunction. In people a major breakthrough in the understanding of AD was the discovery that a heterozygous or homozygous loss of function in the filaggrin gene (FLG) was found to be significantly associated with atopic dermatitis, and that approximately 50% of all AD cases could be explained by the presence of at least one FLG null allele. The FLG gene is normally responsible for the synthesis of the protein profilaggrin in the granular layer of the epidermis. Profilaggrin performs an essential role in the formation of the cornified cell envelope in stratum corneum keratinocytes and of the epidermal barrier. Even in cases lacking specific mutations in FLG, inflammation associated with AD and increased expression of the cytokines (such as interleukin-4 and -13) can reduce filaggrin expression in keratinocytes leading to a defective barrier function.

Mutations in epidermal proteases that regulate degradation of the stratum corneum and enzymes involved in ceramide production and degradation have been identified in human AD.

Barrier dysfunction has extreme clinical relevance in humans with AD, leading to:

i. increased transepidermal water loss

ii. formation of microfissures, which then provide a portal of entry to pathogens and allergens, and sensitivity to chemical irritant

iii. increased scale which presents a greater surface area for bacterial and yeast adhesion and subsequent secondary infection

iv. increased allergic itch associated with increased percutaneous allergen absorption

v. increased non-allergic itch associated with liberation of inflammatory cytokines from the epidermis (irritable skin), dry skin and increased exposure to environmental & microbial proteases

The clinical importance of barrier dysfunction in humans AD is reinforced by studies showing significant clinical improvement and restoration of barrier function with use of ceramide-containing creams. Ceramides play a crucial role in maintaining the barrier function of the skin and in humans a decrease in skin ceramide content has been found to be related to the severity of atopic dermatitis.

Historically there has been some controversy over whether a similar barrier defect exists in CAD. Studies in dog with atopic dermatitis and normal dogs have shown conflicting evidence for and against the presence of cutaneous lipid abnormalities, and for and against a δ-5 desaturase or δ-6 desaturase deficiency in the skin that may result in altered lipid metabolism and barrier defect as a consequence.

More recently canine studies have shown.

i. The deposition of stratum corneum lipid lamellae in atopic canine skin appeared markedly heterogeneous compared with that seen in normal canine skin. When present, the lamellae often exhibited an abnormal structure. The continuity and thickness of the intercellular lipid lamellae were significantly less in non-lesional atopic than in normal canine skin. (Inman et al 2001)

ii. Increased TEWL (trans epidermal water loss) in non-lesional atopic skin compared with skin of normal dogs (Marsella)

iii. Increased TEWL and decreased ceramide in lesional and non-lesional atopic skin (Shimada et al 2008)

iv. Decreased FLG expression in atopic beagles (constitutive not acquired by house dust mite challenge challenge). (Marsella 2008)

v. Increased TEWL in atopic beagles (non-lesional skin) and increased by allergen exposure.

Currently my thoughts are that breed variation in barrier dysfunction may explain the variable clinical phenotypes eg affect the distribution of allergen penetration, sensitisation and elicitation of disease. If this is true then recognition of phenotype may help us when we come to manage these dogs. We will discuss this further later on when discussing management principles.

Role of the Innate Immune System and Development of Atopic Dermatitis

A variety of defects both genetic and acquired have been identified in the innate immune system in AD and include barrier defects, reduced antimicrobial peptide release, genetic polymorphisms, and dysfunction in pattern response receptors, and diminished recruitment of innate immune cells (polymorphonuclear cells, plasmacytoid dendritic cells, and natural killer cells) to the skin due to reduce chemokine production and a failure to upregulate adhesion molecules required for migration. Some of these defects precede the development of the disease and others develop as a consequence of the disease process and affect AD severity. The skin barrier breakdown creates a portal of entry for pathogens, allergens and toxins. Additionally, AD keratinocytes have an aberrant response to microbes that in addition to the diminished recruitment of innate immune cells to the skin may account for AD patients' susceptibility to pathogens such as S. aureus and cutaneous herpes. The reduced recruitment of cells of the innate immune system may be explained in part by polymorphisms in pathogen related receptors such as TLR2, TLR9, NOD1 or 2. The production of antimicrobial peptides is reduced in AD patients compared to either healthy controls or psoriasis. This is thought to be due, in part, to the Th2 cytokines produced by inflammatory cells, which have an inhibitory effect on keratinocyte production of these peptides and on cornified envelope proteins. Circulating NK cells are significantly reduced in AD patients and are functionally defective. Lastly, AD skin lesions have significantly diminished numbers of pDC compared to other inflammatory skin. pDCs are a critical source for the antiviral type interferons.

Dogs with CAD also show increased carriage of commensal organisms on non-lesional skin compared to normal dogs and have increased susceptibility to microbial overgrowth and infections. It is not yet known whether the same level of dysfunction of the innate immunity exists in CAD.

Environment and the Hygiene Theory

The environment may play a role in the development of the allergy side of atopic dermatitis. Large allergen load at an early age may increase the risk. Again allergen load is increased if skin barrier is poor. Once the allergen penetrates the body the immune system then needs to decide whether to develop tolerance (no disease) or sensitisation (allergy). Genetic factors can push the patient down the allergy pathway however it appears genetics are only half the story and that environmental factors are equally important. The hygiene hypothesis of atopic disease in humans suggests that environmental changes in the industrialised world and life style choices (eg bathing more regularly) have lead to a decrease in microbial contact at an early age and increased percutaneous allergen penetration and thus resulted in the growing epidemic of atopic eczema, allergic rhino-conjunctivitis, and asthma over and above what genetics alone can explain. More recently a modified version of this original hypothesis has been developed. This suggests that it is not just a decreased exposure to all infections that increases risk of atopic disease, but more specifically is related to establishment of intestinal microbiota and subsequent development of oral tolerance in the infant. There is evidence to suggest antibiotics early in life can increase the risk of allergic development. In a nutshell, if our environment is too sterile (both on the skin and in the gut) then our evolutionary well-trained immune surveillance system may over-react to harmless challenge (pollens etc) and create a disease state (hypersensitivity).

SENSITISATION TO ENVIRONMENTAL ALLERGENS MAY REQUIRE A COMBINATION OF GENETIC FACTORS (POOR SKIN BARRIER AND ALLERGY GENES) AND ENVIRONMENTAL FACTORS (ALLERGEN LOAD AND REDUCED MICROBIAL TOXINS)

Triggering Allergic Atopic Inflammation

Sensitisation may involve the development of sensitised T lymphocytes (memory cells) that have homing markers and go back to the skin. On re-exposure to the allergen they are triggered to release cytokines and chemokines (signalling molecules) that trigger inflammation and recruit and activate other inflammatory cells. There are two different types of T cells. The type 2 (Th-2) T-cells initiate the inflammation and lead to isotype switching and the production of the allergen specific IgE. IgE then binds to the immune surveillance cells in the skin (Langerhan cells) and makes them much more effective at trapping allergen and presenting allergen to T cells. IgE also binds receptors on the effector cells in the skin (especially the mast cells). Dimeric and trimeric cross linking of IgE can then trigger the mast cells to release a large host of mediators (including histamine and proteases as discussed during the pruritus discussion)) that creates inflammation, cellular recruitment and itch. The atopic inflammatory cascade is bi-phasic. After the initial Th-2 cascade there is recruitment of the inflammatory epidermal dendritic cells and a Th-1 dominated inflammation takes over. The type 1 (Th-1) T-cells take over from the Th-2 cells at that stage and maintain the inflammation. This transition from acute to chronic atopic inflammation occurs very quickly, within about 36 hours, of the initial flare. The ACUTE allergic inflammation (Th-2 driven) progresses at that point to CHRONIC inflammation (Th-1 driven). Most clients will think chronic to mean days to weeks NOT 36 hours. The significance of this is that immunotherapy (desensitisation) works to minimise the frequency of these acute Th-2 flares. Once a flare has occurred it is NOT the initialvallergy that maintains the flare in the chronic phase and RESCUE treatment will be needed. Immunotherapy is NOT expected to bring the chronic phase inflammation back under control. If clients do not recognise this and do not understand the urgency of quick intervention when a flare occurs then a poor outcome is expected

> Once sensitisation has occurred allergen re-exposure triggers inflammation. The most important route of allergen re-exposure is THROUGH THE SKIN however both INHALATION and ORAL exposure may also trigger inflammation in sensitised areas).

Triggering Non-Allergic Inflammation of Atopic Dermatitis

If there was one message that you must take home from this session it is that atopic dermatitis is NOT just an allergy. Much of the inflammation associated with atopic disease does NOT involve allergic mechanisms. I have discussed earlier the role of poor barrier function in the development of sensitisation. The role of the skin barrier does not stop there. Dogs with poor skin barriers can develop inflammation due to IRRITANTS that they contact in the environment. Pollens and dust mite debris have enzyme (protease) activity and this can disrupt the skin barrier further and directly trigger itching and inflammation via protease activated receptors in the skin. This means that you can have atopic disease in the absence of allergy (if your innate skin barrier is poor enough). In humans this referred to as intrinsic atopics. It is also true of dogs that we see dogs with clinic disease indistinguishable from CAD where no allergen specific IgE can be identified.

Allergic inflammation and self-trauma will also cause the skin barrier to worsen leading to drying out of the skin and increased risk of irritable reactions contributing to the overall itch. Shampoos can be a big cause of irritable reactions in inflamed skin so we need to be very aware of this when choosing whether or not to utilise shampoos in dogs with inflamed skin.

We need to be aware that it is not all about IgE. The contribution of IgE and non-IgE mediated mechanisms of inflammation may vary from case to case and this I would expect to account for some of the variability in responses to allergen specific immunotherapy that addresses the allergic aspects the disease only.

Role of Infection Increased Risk of Infections in Atopic Dogs

Staphylococcal spp bacteria and *Malassezia spp* yeast are normal residents on dog's skin. The skin has strategies (exfoliation, antimicrobial peptides, skin lipids, sebum, IgA) to control the numbers of these organisms and in return a stable population of resident bacteria essentially protect us from colonisation by other opportunistic organisms. This balance changes with atopic inflammation due to the "climate" on the skin surface becoming more favourable for microbial overgrowth and a switching off of some of the skin's protective mechanisms due to the inflammation. Dogs may, like humans, have innate and acquired immunological dysfunction that contributes to this overgrowth. The nett effect is that bacterial and yeast colonisation and/or infection of atopic skin is common. The role of infection on atopic skin is significant. These organisms produce proteases (enzymes) that disrupt the glue that hold the skin barrier cells together and thus cause severe barrier dysfunction. Barrier dysfunction results in more allergen and irritant absorption into the skin. Infections cause inflammation and itch potentially via superantigen formation, IgE reactions, compliment activation AND potentially by direct protease activation of PAR2 receptors. Infections have many tools to create inflammation and itch and are often the DOMINANT part of the atopic lesion.

PRINCIPLES OF MANAGEMENT OF CANINE ATOPIC DERMATITIS

CAD is a far more complex disease than we previously thought and the more we know the more we realise this still much we do not know. What seems apparent is that more than one pathophysiologic pathway can create the "atopic" clinical picture. Barrier dysfunction, irritable skin, microbial proteases, IgE and non-IgE mechanisms with genetic and environmental modification all combine to create the atopic picture. CAD is not "just an allergy"!

The major clinical symptom in atopic dermatitis is pruritus (itch). This can impact not only on the quality of the dog's life but also on the enjoyment of owning a dog. If we are to successfully manage dogs with atopy we need to address ALL the mechanisms of itch including itch due to barrier dysfunction (itch from dry skin, irritants, environmental proteases), itch due to infections (IgE mechanisms, compliment cascade, microbial proteases) and itch due to the allergy itself (IgE and non IgE mechanisms and allergen dependent and independent upregulation). Pruritus then becomes a complex interplay of numerous neurochemical mediators. We must also be cognisant that the contribution of barrier dysfunction, infections and allergy will be variable among our patients and that barrier dysfunction may be acquired due to inflammation. Identifying what mechanism(s) are involved in each individual patient is the art of dermatology.

Even though the signal to make you feel itchy usually starts in the skin the signal must be carried by afferent nerve fibres from the skin to the spine, then up the spine to the brain. Ultimately it is the brain that itches not the skin itself. This means that not only is the generation of the pruritic signal complex but also spinal and central processing will affect the quality of the itch and the patient's temperament will affect the response to that itch.

The pruritic response (lick, scratch, rub, roll, chew etc) will vary with the intensity of the itch and the temperament of the patient and be modified by other competing environmental signals. Pain fibres and itch fibres compete for the same pathways in the brain. When a pain signal is carried to the brain an inhibitory signal is sent back that blocks itch fibres. Scratching, chewing, biting behaviours are designed to create mildly painful stimuli that counteract the itch. The more painful the stimulus the longer the itch relief. Rubbing, rolling and licking behaviours are stimulating pressure fibres over a large area of skin and the end result is more temporary inhibition of the itch.

Other than pruritus the major atopic symptoms are recurrent infections skin and ears. These infections are usually surface colonisation or superficial infections although in some breeds recurrent deep infections occur eg muzzle and interdigital dermatitis where there may be concurrent mechanical factors.

1. Establish Baselines

a) Pruritus Score

If pruritus is the symptom that we are trying to control then we need to try and establish an objective baseline measure of itch so we can assess efficacy of our treatments. This is remarkably hard to achieve as our clients tend to be very subjective. As a general rule, a comfortable level of itch is a dog who exhibits pruritic behaviour of low intensity, terminates that behaviour spontaneously after 15 to 60 seconds, gets relief and therefore does not need to repeat that behaviour, at the same site, for several hours. This level of itch does not require intervention. Where the itch signal is strong enough for a dog to interrupt their walk, play, eating or sleeping behaviour to scratch OR where the pruritic episode is intense and includes vocalisation or needs to be physically interrupted to terminate, OR is prolonged > 60 seconds OR frequently repeated, then intervention is required. A scoring system I like is a ***Client Itch Grading Scale Adapted from Hill, et al 2007****:* I have this printed on the clinic wall and EVERY consultation I will ask the client to score the itch level of their dog. As prospective scoring is likely to be more accurate then retrospective scoring I will often print this form and ask the clients to fill in over a 7 days period and fax the results back. This helps me understand the severity of the itch and the need to intervene. Most importantly it is a useful monitoring tool for assessing therapeutic responses. Anything above a grade 2 means that we need to intervene or modify treatment.

- Grade 0: Normal dog itch: The dog does not itch more than before the disease began.
- Grade 1: Occasional episodes (<5/day) of itching: Episodes are of short duration (<1 minute) and do not interrupt normal behaviour.
- Grade 2: More frequent episodes (< 10/day) of short duration (<1minute) of itching: The itching stops when the dog is sleeping, eating, playing or exercising or is otherwise distracted.
- Grade 3: Frequent episodes of itching some of which are greater than 1 minute in duration. Regular episodes of itching are seen when the dog is awake. The dog occasionally wakes up because of itching but itching stops when the dog is eating, playing or exercising or otherwise distracted.
- Grade 4: Prolonged episodes of itching: Lengthening episodes of itching are seen when the when the dog is awake. The dog regularly wakes up because of itching, or itches in its sleep.The itching can also be seen when the dog is eating, playing or exercising or otherwise distracted.
- Grade 5: Almost continuous itching: The itch does not stop when the dog is distracted, even in the consultation room; the dog needs to be physically restrained from itching.

b) Lesional Scores

The CADESI 03 scoring system (canine atopic dermatitis extent and severity index) gives a score out of 5 for erythema, lichenification, excoriation and self-induced alopecia at 62 body areas and is a validated tool for assessing interventions in canine atopic dermatitis. In routine clinical practice this may prove to be time prohibitive HOWEVER the combining a lesion score with the client itch score gives you a powerful monitoring tool. As a compromise I will generally score the dogs during my physical examination rather than follow the formal protocol eg marked erythema of the ventral interdigital space on 3 of 4 feet (4 x 3 sites = 12) + severe bilateral axillary excoriation and mild lichenification (4 excoriation + 1 lichenification)= 5 x 2 sites =10 If they were the only sites affected then the total score would be 22.

I have not yet had an owner come to me worried about their dog's CADESI score but I have plenty worried about itch level. So for me the itch level score is the most valid tool however the lesion score is useful for supporting that the client itch score is valid.

c) Prednisolone Reliance

My ultimate aim when treating atopic dogs is to have a comfortable patient and minimise their reliance on systemic glucocorticoids and avoid immunosuppressive therapies. Prednisolone reliance can be a useful objective measure. Once INFECTION FREE and BARRIER treatments instigated the RESIDUAL ITCH is what we need medication to control. Where oral medications are required (see discussion on topical treatments later today) establishing the MINIMUM EFFECTIVE dose of prednisolone (the prednisolone reliance PR) can be a useful guide to managing. If we are doing thing well then the PR will reduce. Identifying the PR can be done by giving DAILY oral prednisolone at 0.5mg/kg/day for 7 days (most uncomplicated atopic dogs will settle in that time) then covert to reducing to an alternative day regime if maintaining then twice weekly eg Sat and Wednesday. Then reduce the dose by 25% each 14 days if still maintaining. You are aiming for the lowest dose that maintains the itch score at a grade 2 or less. With allergen specific immunotherapy (ASIT) for atopic dogs we are looking to demonstrate that immunotherapy in fact gives us a marked reduction in PR when comparing the pre-ASIT PR and PR levels after 6 to 12 months on ASIT (Peter Hill will being discussing immunotherapy later).

d) Inter-infection Interval

As recurrent skin and ear infections are common in atopic dogs it is good to document the interval between infections and document that this interval increases with good control of the atopic disease

Baselines are critical to monitoring. We want to be objective and want our clients to be objective. Objectivity gives us the ability to give clients realistic expectations and a way of assessing those outcomes themselves. Ultimately the dogs the do the poorly with CAD are often the owners that are disillusioned and poorly compliant with therapy due to unrealistic expectations and lack of objectivity.

2. Improving the Barrier Function

Moisturising the Skin - Hydrotherapy

Moisture can be returned to the skin by bathing in water. A long rinse cycle when shampooing helps hydrate the stratum corneum (outer barrier layer of the skin). This will rapidly dehydrate unless moisturises are applied post rinsing to hinder evaporation. The mechanical action of washing can be useful for removal of allergens/irritants from the skin, reduction of microbial adhesion sites and reducing the itch due to cooling of the skin.

Moisturising the Skin - Topical Moisturising Agents

Formulations may be shampoos, rinses, lotions, sprays, creams, emulsions and ointments. Each formulation has advantages and disadvantages and selection depends on the type of condition being treated, the surface area involved and the presence of hair.

i. Shampoos

Shampoos are generally drying because of their detergent action but some formulations have sustained-release microvesicles that contain active ingredients. These vesicles have an outer lipid membrane that will bind to hair and skin and breakdown to release their contents having a moisturising effect. Ingredients in shampoos that may help moisturise are fatty acids, lipids, urea, glycerin, colloidal oatmeal and chitosanide e.g. Epi-soothe Spherulites® ,(Virbac) which incorporates oatmeal and chitosanide; Allergroom® (Virbac) with spherulites that contains glycerine, lactic acid, urea and chitosanide. Shampoos should not be relied upon as the sole moisturising treatment except in very mild cases. It should also be remembered that even "non-irritant" shampoos may irritate skin with a dysfunctional epidermal barrier. Not all dogs are improved by shampooing!

ii. Lotions, Creams, Ointments

Lotions are liquids with the active ingredients dissolved or suspended. If mixed in an alcohol base, they are drying (eg Dalacin T). Moisturising lotions often contain propylene glycol and water. They may also deliver therapeutic agents. An example is Resisoothe Lotion® (Virbac) which incorporates oatmeal. Lotions have a longer action than shampoos but shorter duration then creams and ointments. For lichenified skin they are probably inadequate. Alpha keri lotion (fractionated lanolin and mineral oil) is very useful for application after shampooing. It is easily applied to large areas.

Dry, lichenified skin is best treated with Hydraderm (sorbolene cream and hygroscopic agent glycolic acid). As the water evaporates, it leaves an oily film on the skin and glycolic acid will draw water from the dermis and trap in the stratum corneum).

Ointments and oily creams are more occlusive which facilitates hydration of stratum corneum and increases penetration of the incorporated active ingredient. Their disadvantage is that they occlude the hair follicles and may produce a folliculitis. They are too greasy to apply effectively on large areas of hairy skin.

Fatty Acid additives in topical preparations can decrease transepidermal water loss to stop the skin drying out. The skin also incorporates some circulating lipids such as plant sterols, essential fatty acids, polyunsaturated fatty acids and arachidonic acid. An example is Megaderm® (Virbac) which contains omega 3 and 6. Dietary supplementation of omega 6 fatty acids may assist barrier repair although appropriate studies to validate this are currently lacking. There is evidence though that the addition of both omega 3 and omega 6 fatty acids to the diet may reduce steroid reliance in atopic dogs. Omega 3 fatty acids become incorporated in the T-cell membranes (TCR) and may modulate T-cells directly. The action of fatty acids may be more than the presumed down regulation of pro-inflammatory eicosanoids. During inflammation there is release of arachidonic acid from the lipid layer of cell walls that results in formation of pro-inflammatory eicosanoids (this is what the non-steroidal anti-inflammatory drugs try to block). Eicoansoids are also liberated from inflammatory cells like the mast cells. The eicosanoids recruit more inflammatory cells to the skin, they augment itching by making the itch fibres more sensitive to the other itch mediators that are being released. Fatty acids of the omega 3 (fish oils and some vegetables) and omega 6 (vegetable oils like safflower oil) when given in the diet will compete with the enzymes forming the pro-inflammatory eicosanoids and lead to the production of less inflammatory eicosanoids. The nett effect is a reduction in the severity of the inflammation. Maximum benefit from fatty acid supplementation may be 8 to 12 weeks. Reported ‘effective” doses vary from 50 to 150mg/kg for omega 3 fatty acids. Eicosaderm ® is the most concentrated form of omega 3 fatty acids available.

Future Treatments for Barrier Repair

You will have to wait until next lecture!

3. Controlling Infections

Both human and canine atopic patients show a tendency to more commonly develop secondary infections. Dogs commonly develop secondary bacterial (particularly *Staph intermedius*) and Malassezia (particularly *M. pachydermatis*). Recent evidence suggests that components of the innate immune system not only protect against microbial invasion, but also contribute to the inflammation of atopy. Further, atopics tend to develop a Th-2 skewed T-cell immune response, which suppresses the anti-microbial immune response. The combination of impaired immunity and microbe induced innate and adaptive immune responses drives a cycle of skin inflammation.

Microbial colonisation may exacerbate the atopic inflammation via numerous mechanisms including IgE responses to bacterial and fungal proteins, T-cell activation by bacterial superantigens and microbial PAMPs (pathogen associated molecular patterns) activating the immunological response via TLRs (toll like receptors). Importantly microbes may cause itch due to protease liberation that is independent of immunologically triggered itch cascades. Clinical experience indicates that controlling microbial colonisation and active infection in some atopic dogs can dramatically reduce the intensity of the atopic lesion and reduce pruritus and reduce steroid reliance.

How to control infections is a lecture on its own (See Beth McDonald’s Management of Infections in the Atopic Dog later today).

4. Controlling the Allergy

Avoidance

Avoidance is not likely to be effective for airborne allergens like pollen as these allergens are widely dispersed in both indoor and outdoor environments. Climatic conditions including wind velocity, humidity and variables such as pollution levels and environmental activity (including vehicular movements) can all affect pollen dispersion. We have no control over these factors. Avoidance may be possible though for dogs with dust mite allergies and grasses that are ground pollinators.

Avoidance may also be useful for dogs with "grass allergy". Clients will sometimes observe that the dogs flare quickly after contact with grass. The distribution affected correlates with contact areas so the distribution may vary in dogs depending on coat type. Although well recognised, the actual pathomechanism is poorly understood and probably involves IgE mediated, DTH and irritant contact pathways. Avoidance may be useful in these cases eg environmental isolation versus lycra suits.

Based on studies in dogs and humans, it is be possible to control dust mite allergies with aggressive control of dust mites in the environment, or total avoidance of going indoors at all. However, this is not always practical in the domestic situation. It could be expected though, that if exposure of allergic pets to dust mites can be reduced at least partly, then response to other therapies, including ASIT, is likely to be better. Strategies include:

- complete exclusion from human bedrooms as dust mite counts are high in bedrooms.
- pets sleeping at night in a non carpeted room to try and reduce nightly dust mite exposure.
- pets sleeping on a suspension bed with a synthetic material (e.g. 'shade cloth' type with aluminium frame) as they do not accumulate mites.
- pet bedding using cotton sheets only. Rugs can blankets can harbour dust mites, and even the dead bodies of the mites can still trigger the allergies in most dogs. Mite bodies are more easily washed from sheets.
- weekly hot wash (> 55°C) of pet bedding. This kills the dust mites.
- weekly vacuuming of the home with a vacuum cleaner with a fine particle filter (e.g. HEPA filers or double bagged vacuum cleaners). Dust mites pass through the filters of average

vacuum cleaners. There is no benefit to vacuuming more frequently.

- steam cleaning of the carpets and cleaning the ducted heating at the commencement of the process may also be advantageous.

Allergen Specific Immunotherapy (ASIT)

This is again a huge subject. Identification of allergens and strategies for immunotherapy will be covered later by Peter Hill.

Non - Allergen Specific Treatments (Pharmacotherapy)

Pharmacotherapy is usually required together with ASIT, at least in the short to medium term, and may be needed long term. It is important to document the level of drug reliance at the start of immunotherapy so that we have an OBJECTIVE measure of ASIT response. It is also important to give the owner's realistic expectations eg give them guidelines as to what are the expected outcomes of immunotherapy eg target levels for drug reliance and at what point do we make a determination as to whether this is a satisfactory outcome. Most clients struggle with the concept that atopic dermatitis is a LIFE-LONG disease and that management will be life long. The benefits of drug minimisation with ASIT are the long-term health benefits. Clients must also be made aware of HOW medications work and why some of the safer medications eg antihistamines are less likely to be effective. Remember that histamine is a small player in the big overall picture of pruritus and there are a paucity of pharmacokinetic studies done in dogs for the antihistamines we use.

Of the drugs that have good evidence for their use in atopic dermatitis we have only glucocorticoids and cyclosporin while there is moderate evidence for the use of pentoxifyline and misoprostenol and little support for the use of antihistamines. The side effects of glucocorticoids are problematic where supraphysiological levels (> 0.1 to 0.2mg/kg) are given frequently and cyclosporin causes broad spectrum suppression of T-cell functions making it less ideal for life long therapy and probably not compatible with ASIT.

Recently there has been a re-birth of interest in topical therapies for dogs with regional atopic lesions where the coat type allows for topical application. Topical glucocorticoids can be effective and offer more targeted treatment with less systemic side effects (we will cover these in the next hour).

Cyclosporin is indicated for severe CAD where the co-ordinated approach is not able to minimise oral glucocorticoid levels to a “safe’ level for long term use. In these case the risk versus benefit is warranted and the safety profile appears much better than some of the other immunosuppressant therapies such as azathioprine.

CONCLUSION

Set baselines and address all aspects of the atopic disease, not just the allergy. Controlling the infection, barrier repair, avoidance strategies and ASIT combined with owner compliance is a great recipe for an atopic dog.

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NOTES:

Chapter 19

Advances in Topical Therapies in the Management of Atopic Dermatitis

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WHAT'S ALL THE FUSS?

In recent times there has been a change in the paradigm of how many dermatological diseases are managed. A constant improvement in our understanding of dermatological diseases, especially atopic dermatitis, in people and dogs is driving a revolution towards increasing use of topical therapies. Three areas in particular are the focus of these changes:

1. Barrier role of the skin and its dysfunction in atopic dermatitis
2. The role of the keratinocyte in cutaneous inflammation
3. The role of microbial colonisation, especially in atopic dermatitis

1. BARRIER DYSFUNCTION

The anatomical/physical barrier of the skin consists of two parts. Some of this barrier function resides within the stratum corneum, but once this barrier has been breached the tight junctions found at the level of the stratum granulosum between the keratinocytes are the next level of defence. The first epidermal barrier is created by epidermal cornification, the end point of epidermal differentiation. An effective epidermal barrier requires intricate organisation and formation of the keratin intermediate filaments and the intercellular lipids together with tight regulation of desquamation, in addition to effective tight junctions. There is significant evidence for both innate and acquired barrier defects in atopic humans and dogs. It is thought that in humans (and likely in dogs) that inherited innate barrier function defects are a (if not the) major primary risk factor for atopic dermatitis. The significance of a defective epidermal barrier is that it loses water through the skin resulting in itchy dry skin with loss of skin flexibility, allows increased penetration of irritants and potential allergens (esp. dust mites) through the skin and has a lowered ability to prevent microbial colonisation. With increased allergen penetration, there is increased exposure of the immune system (via Langerhans cells), thereby increasing the likelihood of development and IgE -mediated exacerbation of cutaneous inflammation.

Barrier repair is a fundamental element of management of atopic dermatitis in humans, but whilst this is not as practical in our veterinary patients and is a major current therapeutic challenge, it remains an important goal.

Evidence for Innate Barrier Changes In Atopic Dermatitis

i. Increased TEWL and decreased ceramide in lesional and non-lesional atopic skin. Ceramides (sphingosines) are major building blocks of the intercellular lipid layer. The reduction of ceramides affects organisation of other lipids within the extracellular space.

ii. Abnormal lipid lamellae in the intercellular space seen on electron microscopy. The lipid lamellae are essential to the skin's ability to prevent penetration of both hydrophilic (most allergens) and hydrophobic substances through the skin.

iii. Decreased expression of filaggrin in atopic Beagles and humans. Filaggrin (FLG) is a keratin filament-associated protein necessary for organisation of the keratin intermediate filaments. FLG and keratin both undergo proteolysis during cornification and form acidic substrates that are hygroscopic (trap water) and also affect pH dependent enzymes involved with desquamation. Lower or defective FLG reduces the ability of the epidermis to trap water, and increases the rate of breakdown of the cornified layer by causing premature breakdown of the corneodesmosomes that hold the corneocytes together.

iv. In humans (but not yet documented in dogs) mutations have also been reported in claudin-1, an important molecule present in tight junctions.

Causes of Acquired Barrier Changes in Atopic Dermatitis

i. Inflammation leads to increased water loss. In humans, the Th2 cytokines IL-4 and IL-13 can both reduce FLG expression.

ii. Microbial proteases cause increase breakdown of corneodesmosomes. Dust mites proteases also have been reported to directly trigger inflammation in the epidermis potentially leading to interference with barrier homeostasis, and to cleave tight junctions.

iii. Surfactants (shampoos, soaps) can increase the pH of the skin leading to increased activity of the enzymes involved in breakdown of corneodesmosomes. This is well documented in humans but less well documented in dogs.

2. THE ROLE OF THE KERATINOCYTE IN CUTANEOUS INFLAMMATION

Innate immunity is the first line of defence against microbes and can be rapidly stimulated (far more quickly than adaptive immune responses) once molecular recognition occurs. This recognition is directed towards unique and widely distributed molecular patterns in microbes, all of which are highly conserved and are crucial to microbe survival (e.g. Gram negative bacterial lipopolysaccharide, bacterial CpG, yeast zymosan). These so called “pathogen associated molecular patterns” (PAMPs) are expressed solely by pathogens of the same class. The PAMPs are recognised by specific host pattern recognition molecules including Toll-like Receptors (TLRs) and nucleotide-binding oligomerisation domain containing proteins (NODs). These bind to either native or opsonised pathogens at extracellular sites and can stimulate destruction via complement activation.

These molecules on the surface of keratinocytes, once bound to microbial PAMPs, act as ‘danger signals’ leading to keratinocyte activation. Similarly, environmental irritants, shampoos and exogenous environmental proteases can all activate keratinocytes to participate, and modulate, the immunological response. The result of this activation is induction of the keratinocytes as an augmentor of inflammation.

There are several consequences to this activation.

a. Activated keratinocytes produce pro-inflammatory cytokines and can even express MHCII and act as antigen presenting cells.

b. Activation of keratinocytes via cytokine receptors (IL-1), growth factors and the TLRs promotes proliferation and clinically identifiable lichenification of the skin.

c. Epidermal inflammation also results in proliferation of inflammatory epidermal dendritic cells that may capture antigen and promote ongoing Th1 driven inflammation to flow on from the initial Th2 atopic cascade.

Much of the cutaneous inflammation seen in atopic disease is driven by EPIDERMAL events. It seems logical then to treat with topical treatments.

3. THE ROLE OF MICROBIAL COLONISATION IN ATOPIC DERMATITIS

It has been well recognised that the skin of atopic humans and dogs shows increase microbial colonisation. There are multiple causes for this:

a. Reduced release of antimicrobial peptides such as defensins and cathelicidins from inflammatory cells and keratinocytes (humans)

b. Greater adherence of staphylococcal bacteria to atopic keratinocytes

c. Localised defects in barrier function

d. Altered microenvironmental humidity

e. A Th2 skewed immune response suppressing an effective anti-microbial immune response. This may be further skewed by TLR2 defects in keratinocytes resulting in weak signalling.

There are several potential consequences of increased microbial colonisation in atopic dermatitis:

a. Bacterial exotoxins can act as superantigens to upregulate T-cell responses, promote IgE production and worsen pruritus

b. Microbes present multiple virulence factors capable of interfering with the host barrier function (e.g. S. aureus produce virulence factors with proteolytic activity, staphylococcal toxins can cause the loss of keratinocyte desmosomal adhesion in the superficial epidermis)

c. IgE mediated hypersensitivity to both *Malassezia* sp. and *Staphylococcus intermedius* has been demonstrated in dogs

It is clear that microbial colonisation can profoundly influence to the course of atopic disease. Topical control of microbes, both directly with antimicrobials and indirectly through modification of epidermal inflammation can help ameliorate clinical signs of AD

WHERE DO TOPICAL THERAPIES FIT INTO THIS?

With management of any disease in veterinary patients, especially chronic diseases such as atopic dermatitis, there are four major therapeutic considerations: efficacy, safety, practicality (and thus compliance) and cost. With good patient and client selection, topical therapies can help achieve many of these goals.

Efficacy

The skin is one of the few organs that can be treated topically. This means that we can often achieve much higher drug levels in the target organ than would otherwise be possible leading to a faster therapeutic response when treating surface infections. For example, parenteral enrofloxacin in a chronically *inflamed* horizontal ear canal can achieve a concentration of just over 9 µg/g tissue, compared with a concentration of 5000 µg /ml enrofloxacin in topical Baytril Otic – over 500x the concentration! Enrofloxacin concentrations are even lower in *normal* skin after parenteral administration. This is especially important for concentration dependent drugs such as enrofloxacin or gentamicin.

Using a different family of topical and systemic therapies together can provide a greater overall efficacy. For example topical mupirocin together with systemic enrofloxacin, will provide a greater spectrum of antimicrobial activity and avoid treatment failure due to any possible partial or complete antibiotic resistance.

Safety

There are typically many fewer systemic effects for topical medications as many of them are either not absorbed at all, or metabolised locally in the skin leading to reduced systemic exposure. One useful consequence of this is the short withdrawal time for topical glucocorticoids prior to intradermal testing in allergic dogs – 14 days in most cases, though one study examining

Mometamax found 17/20 dogs tested satisfactorily 7 days after the end of treatment in cases of unilateral otitis treated at the label dose.

Long-term safety is especially important for glucocorticoids where systemic side effects are can be extremely significant. Glucocorticoids can cause localised side effects (hair loss, loss of elasticity, comedone formation, thin skin, easy bruising and tearing) and with chronic use these must be monitored for, especially in thin skinned regions and in cats. While more modern second generation glucocorticoids have an improved risk:benefit ratio (including mometasone), the diester glucocorticoids (including methylprednisolone aceponate and hydrocortisone aceponate) that show the fewest long term localised side effects. However even with excessive use these can still cause problems. Combination of low dose systemic and low dose topical steroids may be effective in preventing side effects of either used alone.

1. Steroid sprays and lotions may worsen barrier dysfunction in dry skin because they contain alcohols as part of their vehicle that can further de-fat the epidermis.
2. All steroid containing treatments can worsen skin barrier by reducing epidermal lipid formation in the granular layer. Glucocorticoid therapies should be combined with barrier treatments.
3. Be careful when shampoo is applied to inflamed skin. The shampoo vehicle may be part of the problem and not the solution. Ensure owners are vigilant to ensure that the dog is improved after shampooing e.g. no increased itch, no increased redness on the skin, increased scaling or greasiness within 48 hours of washing. Beware dorsally orientated greasiness, scaling, hyperaesthesia or recurrent folliculitis (owners may call it “hives” in short coated dogs) that appear within a couple of days of washing as these may be clues of shampoo triggered irritation. Note though that these are non-specific signs so they should respond to withdrawal of shampoo therapy. If not then they may be secondary to other problems. It is often best to dilute the shampoo before applying to help prevent shampoo irritation.
4. It worth noting that cutaneous absorption of medications (and hence side effects) vary with anatomical site. For example in humans, the scrotum has 12-40x absorption! In cats long term ear medication can cause cutaneous thinning in the pre-auricular region.
5. Oily substances may cause an occlusive folliculitis. This may be seen on the pinnae with ear drop medication.

Practicality

Practicality for most topical medications means that application on thickly haired regions is difficult (some lotions notwithstanding). This is ironic because absorption of many topical medications is BETTER in follicular skin as the follicle and sebaceous gland can act as a shunt past the stratum corneum which is difficult to penetrate, and can act as a drug reservoir for some topical medications. Importantly, there is evidence in humans to show that pollens may also penetrate the skin faster via the follicular pathway.

The practicality of topical applications is dependent on the compliance of the pet and the owner. It is important to understand what both the owner and the pet can tolerate to ensure maximum compliance. If several medications are being used at once, then a calendar may be useful to write down what is given and when. Demonstration of the technique of application is essential e.g. ear drops, use of sprays, treating haired areas with lotions.

Cost

The cost of topical medications is much less than systemic in larger breed sizes. Consideration needs to be given to bottle size to match the dosing frequency. For example a small cortisone spray bottle will run out very quickly compared to a cortisone in a larger bottle e.g. triamcinolone spray (soon to arrive on the market).

When to Consider Topical Treatments in the Consult Room

There are several considerations guiding the clinician as to the appropriate of use of topical therapies. These include correct diagnosis of the disease factors, the patient and client compliance.

Disease Factors

The following are amenable to topical therapies:

1. Lightly haired region, in a repeatable location
2. Fold areas – lip fold, tail fold
3. Surface infection e.g. pyotraumatic dermatitis (hotspots)

4. Flexural areas e.g. cranial elbow flexure
   i. Superficial inflammation - diester steroids only useful for superficial (epidermal) inflammation
   ii. Deeper inflammation – requires a steroid that can penetrate into the dermis
5. Suspect barrier dysfunction – clinically dry skin, nucleated corneocytes (premature desquamation), distribution of disease (eg. contact areas affected, generalised disease)

Patient Factors

Patients that lick off ointments readily means use of an E-collar for 10-15 min, or distracting them by feeding or walking may be required to allow sufficient time for topical therapy to absorb. Some patients are also particularly sensitive to systemic medications and being able to use topicals is a preferred alternative.

Client Factors

Compliance relies on their available time to spend on topical treatments. Lower frequency may be achievable such as once daily. Consider all other treatments and frequencies. Counselling the owners about the reason for use of topical medications i.e. avoidance of side effect attributable to systemic medication, can often achieve better compliance.

USE OF TOPICAL MEDICATIONS IN ATOPIC DERMATITIS: STEPS TO MANAGEMENT

Control Infection

Due to the frequency that infection (surface, superficial and deep) occurs in atopic dermatitis many of the cases present complicated by infection. Controlling the infection should be the first step in management. Due to the ability of infection to further impair barrier function and exacerbate pruritus, it is not possible to assess the severity of the allergic component of the disease or the atopic phenotype until infection is resolved. Lesion scores and itch scores, as discussed last lecture, are done AFTER infection has been resolved.

Treatment of infection is determined by results of cytology and clinical diagnosis of microbial overgrowth VERSUS true superficial infection e.g. folliculitis. The former requires topical treatment and the latter systemic. Surface infections respond quickly, so reassessment after 7 days is recommended including repeat cytology. If the infection has resolved, but the inflammation persists, then you will need to control the epidermal inflammation (see below). Controlling the residual atopic inflammation may be enough to prevent re-colonisation by microbes however preventative maintenance is often employed in the early stages. The management of infections in atopic dermatitis will be covered by Beth McDonald later today and I will only briefly mention topical treatments here. They are not necessarily new treatments but our desire to use these products is.

Table 19.1. Surface Infections Treatments

Cocci	Yeast	Rods	Filamentous rods (anaerobes)
Fucidic acid (*Fuciderm®),*	Clotrimazole 1% cream (Canesten®)	Gentamicin sulfate/betamethasone valerate (Gentocin spray®)	Clindamycin cream 2% (*Dalacin V®)*
Clindamycin cream 2% (*Dalacin V®)*	Acetic acid 2%/boric acid 2% (aqueous solution and wipes) (Malacetic wipes®)	Acetic acid 2%/boric acid 2% (aqueous solution and wipes) (Malacetic wipes®)	Clindamycin lotion 1% (*Dalacin*
*T®)*Clindamycin lotion 1% (*Dalacin T®)*	3% chlorhexidine, 0.5% climbazole, phytosphingosine salicyloyl 0.05% Douxo PS pads *	Biguanide/quartenary ammonium F10 (gel and wipes)	Metronidazole 0.75% gel (Metrogel®)
Mupirocin cream 2% (Bactroban®)	1% acetic acid, 2% boric acid, .15% ketoconazole, 1% hydrocortisone (Malacetic ultra) *	Triz EDTA	
Mupirocin ointment 2% (Bactroban®)			
Biguanide/quartenary ammonium F10® (gel and wipes)			
3% chlorhexidine, 0.5% climbazole, phytosphingosine salicyloyl 0.05% Douxo PS pads *			

* Not available without import licence

Control Epidermal Inflammation

Topical Glucocorticoids

We has discussed above that the epidermis has a role in driving the atopic inflammation. In humans the atopic keratinocytes release pro-inflammatory cytokines Il-1 (interleukin 1), TNF α (tumour necrosis factor) and GM-CSF (granulocyte macrophage colony stimulating factor) at increased rates. IL-1 and TNFα induce a cellular signal cascade that results release of the nuclear activation factor from it's inhibitory complex and results in upregulation of numerous gene transcription factors. These are genes coding for pro-inflammatory cytokines (IL-1, IL-2, IL-4, IL-6, IL-13, TNFα), chemotaxis proteins (e.g., GM-CSF), cellular adhesion molecules, i.e. intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), AND also enzymes, i.e. phospholipase A 2 (an enzyme responsible for the formation of prostaglandin and leukotrienes), inducible forms of cyclooxygenase (COX-2) and NO synthase (iNOS). All major players in inflammation. By inducing cellular adhesion molecules, pro-inflammatory cytokines and increase epidermal chemokine formation (CCL17, CCL22 RANTES, MCP-1 and CCL27) keratinocytes recruit and localize T-cells to the site of atopic inflammation AND ensure maximal activation of the cells. The epidermis is not a passive bystander in skin disease.

By inhibiting the formation of inflammatory cytokines, glucocorticoids interefere with the activation of a variety of immunologic cells. Glucocorticoids inhibit the activation of dendritic cells which normally stimulate Th2 cells. Moreover, eosinophil and T cell apoptosis increases. Topical corticosteroids, as well as local anti-inflammatory and immunosuppressive effects have antiproliferative, and vasoconstrictive effects. Most of the effects of corticosteroids on cells are mediated by binding of the corticosteroid to its receptor in the cytosol, followed by translocation of the drug-receptor complex to a region of the nuclear DNA known as the *corticosteroid responsive element*, where it is then able to stimulate or inhibit transcription of the adjacent genes, thus regulating the inflammatory process. Corticosteroids also exert their potent anti-inflammatory effects by inhibiting the release of phospholipase A_2 and other derivatives of the arachidonic acid pathway.

Glucocorticoids may also have non-genomic effects. Genomic effects take time to start (30 mins in cell culture) as they involve genetic expression. Glucocorticoids can have some immediate effects due to binding membrane associated receptors and block release of phospholipase A2 and arachidonic acid release. It is likely that TOPICAL steroids reach high enough concentrations to exert both genomic and non-genomic effects while systemic steroids do not have non-genomic effects. There appears to be variability amongst steroids in their ability to exert genomic and non-genomic effects and as the side effects of steroids are largely associated with genomic effects, the increased safety (and efficacy) of methylprednisolone, mometasone and budesonide over the more traditional hydrocortisone, prednisolone and dexamethasone steroid groups may be their non-genomic effects.

Topical glucocorticoids are very effective at shutting down the epidermal events of inflammation. Not all steroids are created equal! The choice of steroid will depend on the severity of the inflammation, the type of lesion. The vehicle affects efficacy. For the same active ingredient ointments > creams > lotions as far as potency goes, due to occlusion and greater penetration. As always we need to consider the risk/benefit ratio.

Side Effects of Topical Glucocorticoids.

Epidermal Thinning

- Number of keratinocyte mitoses is diminished
- Stratum corneum thickness reduced
- Granular layer reduced or absent
- Melanocyte pigment production inhibited
- Reduced Keratin 5 and keratin 14 synthesis
- Inhibited K6/16 synthesis (poor wound healing)

Dermal Thinning - Early Atrophy

- Dermal volume reduced – decreased water content, loss of glycosaminoglycans
- Collagen and elastic fibers unchanged

Late Atrophy (Continuation of the Atrophogenic Process)

- Dermal volume reduced
- Collagen and elastic fibers diminished and abnormally aggregated
- Hypoactive fibroblasts
- Dermal vessels fragile, due to loss of fibrous and ground substance support (capillary fragility)

- Follicular atrophy
- Follicular comedones

Topical steroids may be used once or twice daily in the acute situation. These may include Elocon® (mometasone), Diprosone OV ® (betamethasone isoproprionate), Cortavance ® (hydrocortisone aceponate) , triamcinolone spray (the latter requires twice daily application) and Advantan ® (methyl prednisolone aceponate). The potency of steroids varies and compared to hydrocortisone the following potency is:

- 600 times more potent than hydrocortisone: Diprosone OV
- 100 times more potent: Elocon, Advantan, Diprosone cream or ointment (betamethasone valerate)
- 2-25 times more potent: Aristocort (triamcinolone acetonide)
- Hydrocortisone is considered mild

NOTE: Potency and atrophogenic effects are NOT correlated due to variable affinities for glucocorticoid receptor binding and the complex mechanism of action. Mometasone is very potent but is less atrophogenic then hydrocortisone which has low potency.

Mometasone (mono-ester) penetrates the epidermis poorly and is partially metabolised in the skin. Di-ester steroids (Cortavance and Advantan) may be even safer as they are metabolised by epidermal esterases within the epidermis. Cortavance, although registered for daily application for 7 days only, was evaluated in a 70 day trial as an adjunct for CAD. Dogs in this trial were permitted to continue immunotherapy and fatty acid supplements but not allowed any other concurrent anti-pruritic therapy. 28 dogs were treated (as per manufacturer’s instructions daily (Cortavance 15, placebo 13) for 28 days and then 21 dogs were continued for a further 42 days either daily, every second day or twice weekly. The dogs were monitored by CADESI 03 lesion scores and VAS (itch score). Safety was determined by monitoring blood parameters including ACTH stimulation testing and there were no significant changes at day 0, 28 or 70. No gross cutaneous side effects were noted. Of the 21 dogs that continued until day 70 of the trial, 3/21 required DAILY treatment for maintenance, 7 every second day, 6 twice weekly and 5 require additional intervention. The CADESI scores reduced by 61.4% and the itch scores by 38.8%. The authors comment that coat length did NOT impact of clinical outcome (however there were only 2 dogs out of 28 that had a long coat and only one received Cortavance, the other received placebo). Improvement from baseline was noted by day 14 (a “quite rapid” response the authors suggest but this is at odds with the 7 day registration). My thoughts would be that is trial suggests that there is good systemic safety when used for up to 70 days, that a 14 day response would be considered slow by most clients, that a 38% reduction in pruritus is a bit disappointing and most of my cases this would be an inadequate improvement (clients care less about CADESI and more about itch) and that no conclusions can be made about coat type as there was inadequate numbers of long coated dogs in the trial. Cortavance is a useful adjunct but not a sole therapy for CAD.

What Do I Do

I often talk to clients about RESCUE versus MAINTENANCE. If we have infection free persistent itch and inflammation then I like to treat with a potent steroid for control eg Elocon or Diprosone OV (ointment or cream) DAILY or twice daily, with or without occlusion (see below). This is short term, 7 to 14 days, and I expect improvement within hours. Once controlled, I will generally recommend a di-ester steroid Cortavance or Advantan for twice weekly maintenance (together with moisturisers on the non-steroid days in contact areas). Maintenance should continue at that level if comfortable, low level itch. If no itch for a 14 days period then discontinue the steroid and continue the moisturisers. If flares then repeat cycle eg RESCUE → MAINTENANCE → MOISTURISER

Remember that penetration may be affected by anatomical location. In people there is variability is systemic absorption with topically applied steroids with the genitals and eyelids (30%) and face (7%) and armpits (4%) having the greatest potential for local and systemic side effects. Areas of thin skin like the axillae, groin, umbilical fold and scrotum I would monitor closely for atrophic changes even with the di-ester steroids.

General Rules and Tips

Ointments are generally water in oil and are occlusive. Creams are usually oil in water. Lotions have more water than creams and often have alcohols to allow for quick drying. Gels are variable and may be occlusive or rapidly disappear depending on their chemical nature.

1. The vehicle is as important as the drug you are applying to the skin. Most of the non-shampoo topical treatments come as one or more of a lotion, spray, cream, gel or ointment. Moist, exudative skin is best treated with a cream or carbomer gel. Dry, scaling or lichenified skin is best treated with an ointment (hygroscopic properties and increased contact time). Lotions are good for hairy areas

(far less messy) and are appropriate for areas where the skin is essentially normal – this is not lichenified or too dry. Sprays are good for relatively normal skin where treating larger areas but hair may significantly impede penetration and so are often best use on lightly haired skin OR used more generously on haired skin to ensure penetration through to the epidermis.

2. Severe, focally inflamed and thickened skin can benefit from occlusion where a more rapid response is required as this will significantly increase absorption of the medication. E.g. Elocon ointment followed by gladwrap coverage, then Coflex bandaging - repeat twice daily for 20 to 30 minutes if needed
3. Occlusion can also be useful in some cases where there is a severe 'contact' distribution of inflammation (i.e. areas normally contacting the ground). Perform hydrotherapy (put in the bath for 5 to 10 minutes with just water), dry gently, apply Elocon cream or ointment depending on how dry the skin was, wet an old T-shirt, wring so not dripping but still damp and place wet T shirt on the dog and leave for 20 to 30 minutes. Occlusion and hydrotherapy hydrate the skin and increases penetration of the steroid and gives rapid relief.

Calineurin Inhibitors

Pimecrolimus1%(Elidel®) and tacrolimus 0.3% are topical macrolactam immunomodulators. They bind macrophilin-12 (FKBP-12) and inhibit calcineurin, the same target as that of the systemic immunosuppressant cyclosporin A (CyA). Inhibition of calcineurin phosphatase activity prevents nuclear factor of activated T-cells (NF-AT) translocating to the nucleus to activate transcription of proinflammatory cytokines, including IL-2, IL-3, IL-4, IL-5, IL-10, GMCSF, and TNF-α. Thus, inhibition of NF-AT by pimecrolimus or tacrolimus prevents clonal expansion of T-cells, reduces T-cell survival and blocks the formation of cytokines required for helper T-cell activation. Other immunoregulatory effects may include inhibition of Langerhan cell migration and antigen presentation, inhibition of mast cell degranulation and down regulation of keratinocyte receptors. They are smaller molecules than CyA and can penetrate the stratum corneum after topical application. There is minimally absorbed from the skin, reducing the likelihood of systemic toxicity, and pimecrolimus has a 10-fold greater efficacy than CyA *in-vitro*. Tacrolimus 0.1% (Protopic ®) is reported to be more effective than pimecrolimus In human dermatology for AD. . Adverse events with pimecrolimus treatment have been low and long-term (12-month) treatment safety has been established. Both may cause localised irritation at the treatment site reported as a "burning sensation".

Tacrolimus was used in a trial on localised CAD. 20 dogs were treated on their metacarpi with one side treated with tacrolimus 0.1% and the other with placebo. Treatments were performed twice daily for 6 weeks. 75% of treated areas showed a reduction in lesion scores of greater than 50% with the median being a 63% reduction. Itch was not monitored in this trial. Tacrolimus has also been shown in people to be synergistic with steroid application.

The major benefit of these products is they do not cause any dermal or epidermal atrophy in long-term daily application. I use these products as an adjunct to topical steroids where DAILY treatment is needed long term, especially in areas skin thinning is higher risk (eg axillae and groin) and areas were follicular comedones are problematic eg interdigital areas in dogs that have poor conformation.

Liquorice Root

Glycyrrhizinic acid (Glycyrrhizin), a saponin glycoside, is one of the compounds obtained from the root extract of liquorice. Upon hydrolysis, the glycoside is converted to glycyrrhetinic acid. Glycyrrhizinic acid possesses antiviral properties. It inactivates Herpes simplex virus particles irreversibly. Glycyrrhizinic augments host resistance against Candida albicans following burn trauma, probably by inducing CD4 T cells, which suppress type 2 cytokines produced in burn associated injuries. Suppression of Th2 cytokines is potentially useful in atopic individuals.

1% and 2% topical preparations have been studied in a double–blind clinical trial in comparison with base gel on atopic dermatitis over two weeks (30 patients in each group). Two percent liquorice topical gel was more effective than 1% in reducing the scores for erythema, oedema and itching over two weeks ($p<0.05$). In dogs I have only anecdotal evidence to suggest that it is helpful in mild inflammation and may be a useful adjunct where steroid minimisation is needed.

Once the inflammation has been controlled, treatment for barrier function is important.

Improve Barrier Function

The importance of improving the skin barrier function should not be under-estimated. We have already discussed the profound effect the skin barrier can have on atopic progression.

Recognising Barrier Dysfunction

Allergens triggering IgE responses are hydrophilic. Percutaneous absorption of molecules, including allergens, may vary with region due to anatomical factors including surface microclimate, skin thickness and follicular density. In people, the intertriginous zones, external auditory canal, post auricular region and jaw have higher percutaneous absorption indices compared to other body areas (with the exception of the scrotum). Intertriginous areas, muzzle and external auditory canals are regions commonly involved in CAD. Ease or allergen penetration in these areas may be a determining factor.

A functional epidermal barrier effectively minimises the penetration of both hydrophilic and hydrophobic molecules through the stratum corneum.

Innate epidermal barrier dysfunction is well recognised in human atopic dermatitis and has also been documented in CAD. Poor barrier function increases the size of peptides that can be absorbed through the skin. Percutaneous penetration of allergens through barrier-disrupted skin promotes a Th-2 response (characteristic of atopic dermatitis) and IL-4 inducible IgE was correlated to the degree of disruption. This suggests that barrier dysfunction may play a role in sensitisation as well as the elicitation phase of atopic dermatitis.

Currently we accept that barrier dysfunction exists in CAD and it seems logical that this would impact on allergen penetration. What we do not have is an ability to objectively evaluate barrier function in our patients. This makes what I am about to say highly speculative. The future studies looking at trans epidermal water loss in dogs and allergen penetration in dogs will support or disprove this speculation.

I am suspicious that variable innate barrier function may contribute to phenotypic variation in CAD. The premise being that dogs with restricted regional disease involving moist and intertriginous areas may have a better innate skin barrier than dogs with more generalised disease that additionally involves flexural, contact or generalised areas. If variation in barrier function exists in CAD then it may also follow that dogs with poorer barrier function would be subject to greater non-immunological AND immunological triggers of cutaneous inflammation and may be expected to respond less well to allergen specific immunotherapy (ASIT) as this targets only the immunological aspects of the disease.

Currently I assume that dogs with CAD, who in the absence of infection, have active disease involving contact or generalised distribution will have poorer innate barrier function then dogs with classical (moist areas) or flexural disease. I more suspicious I am of barrier dysfunction the harder I work with the owners to do barrier treatments.

Recently we looked at whether phenotype affected outcome of immunotherapy. Where success was determined as a ZERO systemic glucocorticoid reliance

Classic 67% (33/49) vs Contact 49% (17/35) P=0.11

Classic 67% (33/49) vs Generalised 36% (14/39) P=0.0050,

Contact 49% (17/35) vs Generalised 36% (14/39) P=0.35

Dogs with the classical presentation had a 67% success rate (no need for oral or injectable steroids) and this was significantly better outcome than the generalised group. There was a decreasing proportion of dogs with a successful outcome as the severity of the presumptive barrier dysfunction increased (P<0.01)

When this was re-looked at again this time excluding ALL steroid therapy (including topicals) then:

Classic 35% (17/49) vs Contact 6% (2/35) P=0.0015,

Classic 35% (17/49) vs Generalised 8% (3/39) P=0.0041,

Contact 6% (2/35) vs Generalised 8% (3/39) P=1.00,

In this case dogs with the classical presentation did have statistically better outcomes than both the contact and the generalised cases. This analysis under-estimates success as it required dogs to achieve a 100% reduction in steroid reliance to be successful, Traditionally success is a 60 to 80% reduction in steroid reliance during the first 12 months on allergen specific immunotherapy (ASIT). However, looking at this analysis I would conclude that dogs who present with a classical presentation of CAD have a 67% chance of achieving control without the need for oral steroids and about ½ of those will still require intermittent topical steroids. That dogs presenting with the contact pattern have a 49% chance of achieving control without the need for oral steroids but 88% of cases will require intermittent topical steroids.

That dogs with the generalised pattern have a 36% chance of achieving control without oral steroids and 78% will require intermittent topical steroids. Take home message topical therapy as an adjunct to ASIT is extremely valuable and in fact critical to success in many cases. Without it many more dogs would require oral glucocorticoids and/or immunosuppressant therapies.

Whether aggressive barrier treatments would alter that analysis remains to be seen but in the words of Sam Kekovich " You know it makes sense".

Barrier function may be improved by various topical and systemic therapies. Moisturisers, sphingosine therapies, fatty acids and barrier creams are all useful.

Topical Moisturisers

Occlusive Moisturisers

a. **Bath oils** deposits a thin layer of oil on the skin are applied in the final rinse. These are good for applying all over eg after shampooing. QV bath oil (liquid liquid paraffin) and Alpha keri bath oil (mineral oil, lanolin oil) are useful products.

b. **Lotions** are more occlusive than oils. These are best applied immediately after bathing, to retain the water in the skin, and at other times as necessary. QV lotion and alpha keri lotion, Aveeno moisturising lotion are excellent.

c. **Creams** are more occlusive again. Thicker barrier creams containing dimethicone are particularly useful for those flexural areas and ear pinnae eg Johnson's baby cream

d. **Ointments** are the most occlusive, and include pure oil preparations such as equal parts of white soft and liquid paraffin or petroleum jelly. Useful for stubborn areas like hyperkeratotic elbows.

Humectants (add water the stratum corneum)

a. **Urea 10%** eg Urederm cream. These are good products for very dry skin eg pinnae and lateral elbows,

b. **Alpha hydroxy acids** such as lactic acid or glycolic acid. At higher concentrations these also have a de-scaling or keratolytic action by thinning the stratum corneum. These are used a lot in people as they reduce photoaging but for our dogs probably do not have any benefits above the less expensive treatments mentioned above.

Sphingosines

Phytosphingosine (pro-ceramide) therapies (Douxo shampoo 0.1%, pipettes 1%, spray 0.2%) TWICE WEEKLY. Right now it is hard to know where these belong. In human AD ceramide levels are reduced from 46-53% of total protein bound lipids to 23-28% in non-lesional skin down to 10-25% in lesional skin. Ceramide synthesis in lesional skin is dramatically reduced. A similar reduction in ceramide levels is seen in CAD. Topically applied phytosphingosine does penetrate into the living epidermis in people. Radio-labelling studies have documented incorporation of topically applied ceramides into the intercellular lamellae in people and demonstrated superior barrier repair (after acetone injury to the stratum corneum) in ceramide treated skin. It appears to make sense that applying pro-ceramides to the skin should improve barrier function in our atopic dogs.

Sphingosine receptors have been identified that suggest sphingosine plays a signalling role in the epidermis (and elsewhere) and may help regulate the quality of the immunological response by interaction with T-cells and dendritic cells as well as it's role in tissue homeostasis (regulating apoptosis). Sphingosine has also documented antimicrobial properties against skin commensals. Sphingosine no doubt plays an important role in barrier function of the skin, structurally and immunologically. Studies to demonstrate it's usefulness in the management of canine atopic dermatitis are lacking at this stage (they simply have not been done) but anecdotally they appear moderately useful in most cases and extremely useful in some cases. A French study into the clinical efficacy of Douxo seborrhoea shampoo in the treatment of seborrhoea (81 dogs) did not show superior benefit of another mild shampoo. A 4 week, placebo controlled, trial using of 0.05% phytosphingosine and 3% chlorhexidine shampoo on 5 atopic and 5 non atopic dogs showed that both the shampoo and the placebo reduced bacterial counts post shampooing but had no affect on bacterial adhesion. These studies are simply not asking the right questions.

I think these products will be a useful aid but I doubt they are the final solution. I think there will be some exciting times ahead in the field of barrier treatments.

Essential Six (PAW)

This contains bio-diffusion agent, vegetable oil, neem oil, gelling agent, Rosemary extract, lavandin oil, clove oil, tea tree oil, cinnamomum camphor extract, peppermint extract, Cedrus Atlantic bark extract, curcuma longa root extract, Moroccon oregano extract, Gaultheria Procumbens extract, musk, tocopherol acetate, bisabolol.

This is applied as a pipette every week for 2 months to assess response, Washing is not recommended two days before or after application due to purported diffusion and dispersion via sebaceous glands. Essential six has been shown to increase hydration of the stratum corneum and there are anecdotal reports of good responses in seborrhoea but again a lack of scientific studies in atopic dogs at this stage.

Barazone (Dermcare Vet)

This is not a registered product yet but combines barrier treatment with budesonide (topical steroid) and is likely to be a useful addition in the future.

CONCLUSION

I think this lecture will need to be repeated about 2 years from now. Currently there is a pathogenesis driven scramble to create new products that treat the skin topically and overcome the obvious limitations of our hairy patients. There is no doubt in my mind that current and future studies will objectively evaluate these products and probably lead to a second and third wave of barrier products that are increasingly effective. We currently CANNOT expect to manage atopic dogs without topical therapies. How good will it be when we have even better tools to manage these dogs.

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NOTES:

Chapter 20

Management of Infections in the Atopic Dog

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The incidence of infections on the skin of atopic dogs is higher than normal dogs. The increased incidence of infection in atopic dermatitis is also seen in humans where 90% of people with atopic eczema suffer from *Staphylococcus aureus*. *Staphylococcus* species and *Malassezia pachydermatis* are commonly recognized secondary infections in the atopic dog. *Demodex canis* also occurs and can present a therapeutic dilemma in atopic dogs requiring glucocorticoids.

Canine skin has a relatively thin corneum, a low level of intercellular lipids, lack of a follicular lipid plug and has a higher pH. This facilitates the contact of environmental and microbial allergens to the epidermal immune cells. Licking and scratching further disrupts epidermal barrier function.

Both *Staphylococcus* and *Malassezia*, have shown increased ability to colonize, adhere and penetrate the stratum corneum of atopic dogs compared to normal dogs. Once adhesion and colonization is achieved, these micro-organisms and the toxins they produce, have the potential to induce cutaneous inflammation. The inflammation is triggered by their microbe-specific type-1 hypersensitivity to the organisms, and by the release of exotoxins acting as superantigens.

Demodex canis are commensal acarid parasites that colonize hair follicles. Mites multiple and create significant folliculitis and secondary pyoderma where there is immune dysfunction. This suppression of the immune system may be due to genetic factors, immunosuppressive therapy, endocrinopathies, concurrent infections, neoplastic or metabolic disorders.

STAPHYLOCOCCAL PYODERMA

Staphylococcus pseudintermedius (formerly known as *Staphylococcus intermedius*) is the most important pathogen on dog's skin and is believed to be responsible for more than 90% of canine pyoderma. *Proteus*, *Pseudomonas*, *E. coli*. *Methicillin-resistant Staphylococci* and *Staphylococcus schleiferi* occur less commonly.

(Methicillin resistance implies resistance to all beta-lactam-based antibiotics, including cephalosporins).

Compared to normal dogs, atopic dogs have increased numbers of resident bacteria on their skin that have the potential for conversion to pathogenicity. The growth of aerobic organisms is increased and a greater number of sites (anus, nasal passage) carry increased numbers of *coagulase positive staphylococci*.

Normally, *Staphylococcal* organisms are not considered to have high levels of virulence. The presence of a bacterial pyoderma in the dog should signal underlying primary disorders such as hypersensitivities, parasites, follicular disorders, keratinization defect, or metabolic disease.

Staphylococci produce exotoxin secretory products that act as superantigens. These include enterotoxins A, B, C, D; toxic shock protein; protein A; peptidoglycans and teichoic acids. Superantigens stimulate T-cells, amplify the inflammatory response and triggers release of cytokines from keratinocytes.

There is greater adherence by *Staphylococcus intermedius* to keratinocytes of dogs with atopic dermatitis compared with those of normal dogs via expression of surface antigen molecules, teichoic acid and protein A. These bind to keratinocytes surface receptors fibronectin and vitronectin.

Anti-staphylococcal IgE has been detected in the serum of atopic dogs with concurrent staphylococcal infections.

Clinical Signs

Clinical signs include significant inflammation and pruritus, erythema, papules, pustules, epidermal collarettes, crust and scale, hyperpigmentation and patchy alopecia. Lesions are associated with the trunk, ventral abdomen and chest, intertriginous areas, paws and face. Infection depth varies. Atopic dogs can suffer from surface pyoderma, superficial folliculitis or deep pyoderma. Depth of infection is one of the factors that determines the length of treatment that can be expected.

Breeds with a predisposition to recurrent bacterial infections include Golden and Labrador retrievers, Bull Terrier, Dachshund, Dalmatian, Doberman, English Bulldog, German Shepherd, Irish Setter, Newfoundland, Rottweiler, Shar pei, Shetland sheepdog, and West Highland White Terriers.

Diagnosis

To successfully manage recurrent pyoderma in the atopic dog, it is essential to be able to recognize clinical signs. The differential diagnosis of *Staphylococcal* infection include: dermatophytosis, demodicosis, follicular dysplasia, subcorneal pustular dermatosis, sterile eosinophilic pustulosis, and immune mediated disease particularly, *Pemphigus foliaceous*.

Cytology of intact pustules, impression smears and sticky tape preparations are used to identify the presence of pathogenic bacteria. Intracellular cocci confirm *Staphylococcal* infections and direct that empirical antibiotic therapy is indicated. However, cytological examination of cases of bacterial overgrowth (BOG) will show large numbers or cocci and low to nil numbers of neutrophils. These cases respond very well to antimicrobial therapy. Therefore the phagocytosis of cocci by inflammatory cells should not be considered an essential prerequisite for antibiotic use.

Culture and sensitivity should be considered where there is deep pyoderma, where cytology of pustules show bacteria despite current antibiotic therapy, where bacilli are seen on cytology, or where clinical signs fail to respond to appropriate treatment.

Treatment

Successful therapy requires a combination of therapeutic agents and approaches to control pruritus created by the combination of atopic dermatitis, *Staphylococcal* infections and epidermal barrier failure. If the underlying disorders are not corrected, bacterial infections become chronic and recurrent.

The results of intradermal skin testing or serum IgE levels guides the selection of allergens to be placed in the desensitization program. In addition, avoidance of allergens should be attempted where practically possible. Desensitization significantly resolves the signs of atopic dermatitis in 70 – 80% of dogs. Immunotherapy also decreases the relapse rate of infection. In some cases, desensitization is the sole form of therapy required. More commonly, other therapeutic agents are required, but at lower doses and frequency.

Systemic

Chronic or recurrent pyoderma is often due to an allergic disorder. It is not uncommon that recurrent pyoderma may be the only clinical sign of atopic dermatitis that is expressed. Antibiotic therapy can have a partial to complete resolution of clinical signs. Recurrent pyoderma usually requires long term antimicrobial therapy and these include cephalosporins, amoxicillin clavulonate or fluoroquinolones. Cephalosporins are considered the antibiotic of first choice.

If pyoderma relapses greater than every two months, then a three week course of daily antibiotics can be used. If the relapse rate is less than two months, then a daily dose therapy is used for 1- 2 weeks past clinical cure, followed by suboptimal or pulse regimes (pulse therapy).

Pulse therapy protocols vary. Some use a seven day on, seven days off program. Others find most success giving antibiotics two consecutive days a week. Others reduce daily doses by half and then to every alternate day.

Carlotti (2005) gave pulse therapy two days a week using cephalexin at 15mg/kg twice daily. This significantly extended time between relapse of infection to a mean of 6.6 months in the pulse therapy group compared to a relapse time of only 2.5 months in the placebo control group.

Pulse or intermittent antibiotic therapy could cause more resistance than continuous antibiotic administration and culture and sensitivities should be performed when expected response to treatment is not achieved.

The skin is one of the most difficult tissues in which to obtain high therapeutic antibiotic levels and this is why doses required to control bacterial skin infections are higher than recommended label doses and length of treatment is also prolonged.

Staphyloccocus pseudintermedius is sensitive to various fluoroquinolones (enrofloxacin 5mg/kg once daily), amoxicillin clavulanate (20mg/kg twice daily), oxacillin (20mg/kg three times daily) cephalosporins (20 – 30mg/kg twice daily) and cefovecin at 8mg/kg every 14 days (Convenia®, Pfizer). Reduced but still effective activity against *Staphylococci* is seen to lincomycin (20mg/kg twice daily), clindamycin (5mg/kg twice daily), tylosin (10-20mg/kg twice daily), erythromycin (15mg/kg twice daily) and chloramphenicol (50mg/kg twice daily). Potentiated sulphonamides have limited use with resistance and side effects problematic.

Surface pyodermas (hot spots) require 10 – 14 days of antibiotics. Pyoderma and folliculitis required 3 – 4 weeks of daily therapy (one to two weeks past clinical cure). Deep pyoderma require at least 6 – 8 weeks of therapy (two to four weeks past clinical cure).

Topical

Staphylococcus are among the most resistant of the non-spore-forming organisms. They resist dehydration, are relatively heat-resistant and tolerate antiseptic medications better than other bacteria. Topical therapy reduces bacterial organism loads, water rehydrates skin and shampoos remove tissue debris.

Though the skin is the largest organ of the body and easily accessed by topical therapy, antimicrobial shampoos remain an insufficient form of sole therapy. They are an adjunct to systemic therapy and of value in maintenance. Overuse may result in irritating and macerating the skin via loss of surface lipids and disruption of the epidermal barrier function.

A disadvantage of shampooing is that products are left on for 10 minutes, but then rinsed off and lost. Benefits last only 24 – 48 hours. Recent advances in product formulations now extend topical residual activity by increasing the binding and release of moisturizers and other active ingredients (Epi-Soothe Spherulites®,Virbac; Aloveen Leave-On Conditioner®, Dermcare). To the owner, these advances in formulations, translates to less frequent bathing, yet increased benefit.

Shampoos

There are a range of medicated shampoos available for use in atopic dogs with bacterial infections in Australia.. They include those containing 3% chlorhexidine (Pyohex ®, Dermcare; Pyoderm S®, Virbac), Miconazole 2% combined with 2% chlorhexidine (Malaseb®, Dermcare), econazole, sulphur/salicylic acid, chloroxylenol (Sebazol ®, Virbac) and benzoyl peroxide (Pyoben®, Virbac). A contact time of 10 minutes is recommended.

Thorough rinsing is required. Removal of surface lipids by the action of shampooing will results in changes in transepidermal water loss and barrier dysfunction. This can be corrected by lipid replacement with humectants and emollient moisturizers.

Creams and Lotions

Topical creams/lotions are ideal for localized infections such as intertrigo, callus pyoderma, canine acne and pododermatitis. They can produce a resolution of clinical signs within 10 days. Mupirocin and fusidic acid are the most effective against *Staphylococcal* organisms.

Mupirocin 2% cream (Bactroban ®, GlaxoSmithKline) has excellent penetration into fibrotic tissue and a broad spectrum of action. Fusidic acid is available as a 0.5% formulation combined with betamethasone gel (Fuciderm ®, Bayer). Clindamycin 2% cream (Dalacin V®, Pfizer) also has effect against gram positive and some gram negative organisms.

Triz EDTA ®(Dermapet) chelates the slime capsule that protects and surrounds gram negative organisms such as Pseudomonas. Loss of the capsule makes the bacteria susceptible to otherwise “resistant” antibiotics. Where cytology shows rod shaped organisms, lesions can be cleaned with TrizEDTA prior to application of topical products such as clindamycin.

Treatment Failure

The most common cause of treatment failure is an inadequate dose or inadequate length of treatment, combined with the failure to treat the underlying disorder (atopy). Clinicians may under prescribe antibiotics, but most commonly it is a failure of client compliance, or patient resistance to be medicated, that results in inadequate antibiotic administration.

There is growing emergence of antibiotic resistant bacteria, particularly coagulase negative *Staphylococcus schleiferi* and methicillin resistant *Staphylococcal aureus and pseudintermedius.*

It is important to consider resistance when recurrent pyodermas are present. Culture and sensitivities should be performed and the selection of appropriate antibiotics can then be made.

Immunostimulants or Immunomodulation

A variety of agents have been used to stimulate the immune system in cases of recurrent infections. Levamisole (an anthelmintic) is thought to act via cell mediated immunity, and cimetidine (H-2 Histamine receptor blocker) is thought to inhibit histamine induced immunosuppression. There are no quality studies supporting their use.

Various bacterial products have been used with some success in cases of idiopathic recurrent pyoderma. These products are not available in Australia. *Staphage Lysate* (SPL®, Delmont) is a polyvalent bacteriophage derived from *Staphylococcus aureus*. It is given as a subcutaneous injection twice weekly for three months and then every seven to fourteen days. Immunoregulin (Immunovet) is derived from killed *Propionibacterium acnes*. It is given intravenously twice weekly for two weeks and then weekly as a maintenance dose. Response to these products has been promising.

DEMODICOSIS

Demodicosis can occur in atopic dogs (both conditions involve a T-cell dysfunction) and demodex infections are considered a combination of genetic factors, secondary infections and use of immunosuppressive drugs such as chronic glucocorticoids in the atopic dog.

Breeds recognized as having a predisposition to demodicosis include West Highland White Terriers, Shar Pei, English and French Bulldog, Doberman, Staffordshire bull Terrier, Shih tzu, Boxer, Great Dane and Pug, The distribution and appearance of lesions of atopy and demodicosis (and *Malassezia* dermatitis and *Staphylococcal* pyoderma) share many similarities. These include erythema, folliculitis, secondary pyoderma (and associated secondary pruritus), alopecia, hyperpigmentation and crust associated with the face, paws and trunk.

Clinicians should be cautious in assuming clinical signs of pododermatitis, facial pruritis or alopecia in atopic dogs are due to a flare of their allergic disease. Prior to prescribing anti-inflammatory drugs such as glucocorticoids or cyclosporine, multiple deep skin scrapes must be performed. If glucocorticoids are given to control signs of inflammation and pruritus, and a subclinical demodex infection is present, the resultant immunosupppression may allow the proliferation of the mite and development of clinical disease.

Demodex injai, causes a pruritic seborrhea along the dorsum, mimicking flea allergy dermatitis. Again, without routine and repeated skin scrapes (biopsy may be needed to identify this species) the infection can be missed and glucocorticoids inappropriately administered.

There are atopic dogs that require low doses of glucocorticoids or cyclosporine to maintain a quality of life, despite desensitization, control of secondary infections and support of epidermal barrier function. Some of these dogs develop demodicosis. In these cases, treatment of demodicosis is required and should be expected to be ongoing due to the concurrent need for anti-inflammatory drugs and host immune dysfunction.

Treatment

Treatment of demodicosis involves the use either registered or off-label products. The two available registered products in Australia are weekly Amitraz rinses (Demadex®,Delvet); or monthly applications of moxidectin (Advocate® ,Bayer, Animal Health). Off-label formulations include ivermectin (Ivomec®, Merial) at 400ug-600ug/kg per os daily), doramectin (Dectomax®, Pfizer) at 400-600ug/kg weekly s.c. and moxidectin (Cydectin®, Fort Dodge) at 400ug/kg daily. Milbemycin oxime (Interceptor®, Novartis) is effective at 1 – 2 mg/kg daily. However, in Australia, milbemycin oxime is now formulated in combination with praziquantel and so cannot be given daily.

Ivermectin can create serious adverse reactions in certain breeds of dogs (Rough collies and their crosses) and individual dogs due to MDR-1 gene deletion. Clinical signs include mydriasis, depression, tremors, hypersalivation, inappetance, coma and ultimately, death.

Whichever treatment is used, animals should be assessed every four weeks, a series of skin scrapes performed and mite numbers and stage of life cycle recorded. Treatment is continued for one to two months past negative skin scrapes.

MALASSEZIA DERMATITIS

Malassezia pachydermatis is a lipophilic, non-lipid dependent, nonmycelial saprophytic yeast with a thick walled, oval or peanut shape. It is commonly found on normal and abnormal skin. It is considered part of the normal flora of the ear canals, anus, lips, vagina, interdigital areas and anal sacs.

Malassezia dermatitis appears to have a breed predisposition in the West Highland White Terriers; Cocker Spaniels; Basset Hounds, Labradors, Shih Tzu; English Setter; Dachshund, Springer Spaniel, German Shepherds, Silky Terriers, Maltese, Chihuahua, Poodle, Shetland Sheepdogs, and Lhasa apso. Many of these are also recognized as having a breed predisposition to atopic dermatitis.

Malassezia converts from normal flora to a pathogen under certain conditions. There is an alteration of the microclimate of the skin with humidity, increased surface lipids and loss of epidermal barrier function. These epidermal changes are a consequence of underlying hypersensitivity disorders, endocrinopathies, keratinization defects, parasitic and metabolic disorders.

Atopic dogs can develop a Type-1 hypersensitivity reaction to allergens expressed by *Malassezia* and presented to the immune system once the organism has adhered and penetrated into the stratum corneum. *Malassezia* also produces inflammatory products that alter the sebum barrier of the skin, activate complement and amplify inflammatory reactions. These include various proteases, phospholipases, lipoxygenases, phosphatases and zymogen.

The primary lesions associated with *Malassezia* infections are erythema and pruritus. Secondary lesions rapidly develop and include: rancid odour, lichenification, and hyperpigmentation, hyperkeratosis, traumatic alopecia and adherent yellow scale. The distribution by be localized or generalized with the palmar/plantar surfaces of the paws, claw beds, ear canals, face, ventral neck, flexural surfaces of the forelegs and intertriginous zones (axillae, peri-vulva). Response to antibiotics and glucocorticoids is often poor.

The differential diagnosis of *Malassezia* dermatitis include hypersensitivity disorders (contact, food allergy, atopy), bacterial infections, demodicosis, chronic scabies, neoplastic diseases such as Epitheliotrophic T-cell lymphoma, immune mediated disease such as an adverse drug eruption

Diagnosis

Diagnosis is best made using a combination of response to therapy (topical and/or systemic), recognition of clinical signs, results of cytology and history. In many dogs, identification of organisms from cytology and culture can be poor in the face of classic clinical signs. However, in these same cases, response to treatment, can be remarkable.

Intradermal skin testing is not a diagnostic tool for Malassezia infection. It confirms a Type-1 hypersensitivity reaction to *Malassezia* antigens.

Cytology

There are a variety of guidelines available on the numbers of organisms on cytology that are clinically significant. It is commonly considered that an average of 1 - 3 organisms per high power oil immersion fields (hpf) is consistent with Malassezia dermatitis.

However, we know that in atopic dogs with *Malassezia* hypersensitivity, much lower numbers will create significant pruritus. Morris (2009) recommends antifungal therapy when more than 1 yeast per five high powered fields is seen. He considers numbers significant in inflamed ears at 1 organism/ single hpf. The low numbers seen on cytology in cases where response to therapy is marked, may also be explained by the mechanical action of licking, which strips the surface organisms before they can be harvested for cytological examination.

There are several cytological techniques available. Sticky tape preparations, rolled cotton swabs onto slides, and impression smears (heat fixed) can be collected from the surface of inflamed skin once it is gently clipped. They may be stained with Diff Quik or directly with methylene blue. The organism can have a variable uptake of stain and appearance. Some remain ovoid; others have unipolar budding and appear as having a snow man/peanut shape. They often adhere in clusters to keratinocytes.

Culture using contact agar plates gives quantitative information valuable in research. Many do not consider cultures of value for clinicians when compared with cytology and response to therapy.

Histopathology may not be diagnostic as yeast organisms are often lost in the processing of biopsy samples. When collecting samples, do not prepare the site aseptically prior to the procedure, as the surface scale, lipids and crust contain the organism i.e. do not scrub off the pathology.

A commercial extract of *Malassezia pachydermatis* is produced by Greer laboratories and is available and used in Australia for intradermal skin testing. The threshold concentration is 1,000 pnus/ml (protein nitrogen units).

Therapy

Treatment should be aimed at correcting the predisposing disease (atopic dermatitis), establishing an effective epidermal barrier function as well as using a combination of systemic and topical anti-yeast products to eliminate the infection. Client compliance and patient tolerance are important factors to consider. Therapy is unlikely to complete eliminate *Malassezia* from the skin as it is part of the normal flora and reseeding of the organism from mucosal surfaces will occur during grooming.

In the atopic dog with Malassezia dermatitis, you can get a reduction in pruritus of 75 – 100% simply by treating the *Malassezia* infection. When trying to manage a poorly controlled atopic, undiagnosed *Malassezia* dermatitis should be considered.

Systemic therapy is required to control infection and response to therapy may take one to two weeks. Patients should be assessed every three weeks for response, concurrent reductions in organisms identified on cytology, and to monitor for adverse reactions. Topical therapy is a useful adjunct to systemic treatment, but in general, will not eliminate active infection unless lesions are quite localized. Systemic therapy is based on drugs from the azole group of drugs. These inhibit the fungal cytosol P-450 enzyme of the yeast and prevent the formation of ergosterol, an essential component of the fungal cell wall.

Ketoconazole (Nizoral ®, Janssen-Cilag) at 5 – 10mg/kg daily for 3 – 4 weeks and then pulsed at 5 – 10mg/kg daily, two consecutive days a week. Ketoconazole is presented as 200mg tablets in blister packs of 10 or 30 tablets. The tablets can be relatively easily quartered and less easily split into eighths for dosing dogs 5kg or less. Absorption is enhanced if ketoconazole is given with food.

The incidence of side effects is reported to be around 10% and this incidence increases with a corresponding increase in dosage. Adverse reactions include inappetance and vomiting. Pruritus, alopecia and lightening of the hair coat are reported, but not commonly seen. The risk of hepatotoxicity are significant, and clinicians should be cautious and measure liver enzymes when using doses over 10mg/kg daily long term.

Ketoconazole interacts with many other drugs, of clinical significance is its ability to potentiate the activity of cyclosporine.

Itraconazole (Sporanox®, Janssen-Cilag) at 5mg/kg once daily for 3 – 4 weeks, or 5mg/kg two days a week for 3 weeks. Itraconazole is a triazol with increased potency and decreased toxicity compared to ketoconazole. Itraconazole is available as 100mg capsules. The drug is evenly distributed within the beads inside the capsule. In small dogs, capsule can be opened, and the beads distributed into the food. Itraconazole is keratinophilic and is stored in sebum for prolonged periods allowing the medication to be pulsed rather than given daily. Side effects include vomiting, hepatotoxicity and vasculitis.

Fluconazole (Diflucan®, Pfizer): 2.5- 5.0mg/kg once daily for 3 – 4 weeks; or 5mg/kg daily, two days a week for three weeks. Like itraconazole, fluconazole is a triazol. It is potent and has low levels of toxicity. It persists in the epidermis for 10 days after medication has ceased, suggesting it will be able to used in a pulsatile fashion. Generic formulations have reduced the expense associated with the use of this drug.

Terbinafine (Lamisil®, Novartis) at 30mg/kg once daily for 3 – 4 weeks. Terbinafine is an allylamine not an azole. It inhibits the enzyme squalene epoxidase resulting in a deficiency of ergosterol in the cell wall and an intracellular build up of squalene within the cell, creating cell death. It does not act on the fungal P450 enzyme.

Griseofulvin is ineffective against *Malassezia.*

Glucocorticoids should be avoided. They are immunosuppressive and may create a rebound effect of yeast infections when stopped.

Immunotherapy

A commercial extract of *Malassezia pachydermatis* is produced by Greer Laboratories and is available for use in Australia for intradermal skin testing and subsequent desensitization. The threshold concentration for skin testing is 1,000 pnu/ml (protein nitrogen units). This concentration of allergen is the highest concentration that does not produce positive results in greater than 90% of normal individuals. In Farver's study, 93% of atopic dogs with Malassezia dermatitis had positive intradermal skin test reactions to Malassezia extract. 100% of atopic dogs with Malassezia otitis only, tested positive, but numbers of dogs were low. 31% of atopic dogs without Malassezia infections, tested positive. No normal dogs in this study tested positive at the 1,000pnu dilution. At present, no serum IgE tests can be recommended.

In a recent multicentre study, atopic dogs on immunotherapy, with persistent *Malassezia* dermatitis and pruritus that still required anti-fungal therapy, were given 1,000pnu *Malassezia pachydermatis* allergens, once weekly. Response was excellent in 2 of 4 dogs and the remaining two had a significant reduction in pruritus once *Malassezia* was added to the desensitization schedule.

Topical Treatment

Topical therapy is a useful adjunct to therapy, but in general, will not eliminate active infection. Topical therapy is of more value in maintenance and prevention of relapse. However, irritant or excessive shampooing can disrupt the epidermal barrier function and should be avoided.

Shampoos

Miconazole 2% combined with 2% chlorhexidine (Malaseb®, Dermcare), econazole, sulphur/salicylic acid, chloroxylenol (Sebazol ®, Virbac) and benzoyl peroxide (Pyoben®, Virbac) are the most commonly used products in Australia. Some dogs experience erythema after use, this may be due to release of zymogen from the yeast onto the skin, or due to irritant factors creating inflammation and disturbing the barrier function. A contact time of 10 minutes is recommended and 50mls of Malaseb® is considered sufficient for a 30 kg dog.

Additional anti-fungal topical products are 1% selenium sulfide (Selsun blue®, Church & Dwight) and ketoconazole 1% (Nizoral®, J & J Pacific).

Rinses

1:1 dilution of white vinegar and water is economic and has some efficacy.

Enilconazole **(**Imaverol ®, Janssen) a 0.2% solution is applied topically every 3 – 4 days. This can leave the skin and coat feeling sticky, but does have residual activity useful in chronic or recurrent cases and where repeated shampooing is not practical.

Ointment and Creams or Wipes

These have some use as spot treatments for localized infections such as those found around lip and vulval folds, between the palmar/plantar interdigital spaces and axillae. The most effective products contain miconazole or clotrimazole. They should be applied twice daily for 2 – 3 weeks and then used twice weekly as maintenance.

Topical creams include:

Clotrimazole 1% (Canestan®, Bayer)

Terbinafine 1% (Lamisil®)

Miconazole 2% (Daktarin®, J & J Pacific; Fungafite®, Ilium)

Econazole 1% (Fungazol®, Ranvet) used in horses

Mupirocin 2% (Bactroban ®,GlaxoSmithKline)

Nystatin 1% (Nilstat®Sigma).

Topical wipes containing acetic 2%acid and 2%boric acid (Malacetic wipes®, DermaPet) are effective and easily used by clients.

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Chapter 21

Allergy Testing and Immunotherapy

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Two methods of allergy testing are routinely available for the further investigation of canine atopic dermatitis: intradermal skin testing and in-vitro measurement of allergen-specific IgE (IgE serology). Many practitioners believe that a positive result in either of these tests is diagnostic for canine atopic dermatitis - it is not. Positive results can be obtained with either test in clinically normal dogs and dogs with other skin diseases. The test result is only meaningful if the dog has clinical signs consistent with atopic dermatitis and all other pruritic diseases have been ruled out.

INTRADERMAL SKIN TEST

The intradermal skin test is a method for demonstrating the presence of hypersensitivity to various environmental allergens based on skin reactivity.

Intradermal skin testing is usually performed at referral centres or in practices in which there is a clinician with a specific interest in dermatology. The selection of allergens and interpretation of intradermal skin tests requires specialised advice and training. Allergen solutions are also expensive and it would not be cost effective to offer this service unless one or two tests per week were being performed.

Practitioners interested in performing this procedure should visit a specialist veterinary dermatologist, study for a further qualification in the discipline or undertake residency training. The intention of these notes is to provide veterinarians with sufficient background to the methodology to allow appropriate case selection and to be able to inform clients about the procedure.

Veterinary dermatologists may test for reactivity against the following antigens:

- House dust mite and storage mite antigens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, Acarus siro, Tyrophagus putrescantiae, Euroglyphus maynei).
- House dust (a mixture of dust mite antigens, human and animal danders, bacteria, fungal spores, and fibres).
- Insect saliva or body parts (flea, ant, cockroach, house flies, mosquitoes, moths)
- Pollens (from trees, weeds and grasses).
- Moulds (from the household or from crops)
- Malassezia pachydermatitis

The inclusion of regional allergens (pollens) in the testing kit is based on knowledge of the plants in a particular geographical location.

Indications

Allergy testing is indicated in animals with a history and clinical signs consistent with atopic dermatitis in which allergen immunotherapy is considered the treatment of choice. It should only be performed after other pruritic diseases have been ruled out or controlled (ectoparasites, pyoderma, *Malassezia* dermatitis, food allergy).

Technique

1. The procedure is best performed with the animal under sedation in lateral recumbency. Medetomidine (Domitor) at a dose of 10 - 20 μg/kg is the preferred sedative. Acepromazine (ACP) is not acceptable because it reduces skin test reactivity.
2. A patch of fur is clipped from the lateral thorax (about 15cm x 10cm).
3. The injection sites are marked using a black marker pen.
4. Approximately 0.05 ml of each antigen is injected intradermally along with the positive (histamine) and negative (saline) controls (the exact amount isn't critical as long as all the injections are the same size).
5. The reactions are read 10-20 minutes later. These appear as wheals. The positive control is given a score of 4+ and

the negative control a score of 0. Other reactions are subjectively graded between these values based on the diameter of the wheal, the degree of erythema and the height of the wheal.

6. In some cases, late phase reactions may occur at some sites 24 – 48 hours later. These appear as erythematous, indurated areas that may contain a papular eruption. The full significance of these reactions is currently unknown. Some dermatologists ask owners to observe for these reactions after the animal has gone home.

Interpretation

The skin test is interpreted by correlating the positive reactions with the patient's history. Clinically relevant reactions can then be used to choose allergens for specific immunotherapy.

IgE SEROLOGY

In-vitro testing simply requires a blood sample to be taken and sent off to an appropriate laboratory. The serum is assayed for allergen-specific IgE and the results are reported as relative units (the higher the score, the higher the level of IgE). The tests use either monoclonal antibodies against IgE, or the FcεR1 IgE receptor that is normally present on mast cells, to detect the IgE.

Indications

As with skin testing, IgE serology is only indicated in animals with a history and clinical signs consistent with atopic dermatitis in which allergen immunotherapy is considered the treatment of choice. ***It should only be performed after other pruritic diseases have been ruled out or controlled*** (ectoparasites, pyoderma, *Malassezia* dermatitis, food allergy).

Technique

1. A blood sample is taken and the serum sent off to a laboratory offering the service.
2. The diluted serum sample is added to a plate containing individual wells coated with specific antigens. The range

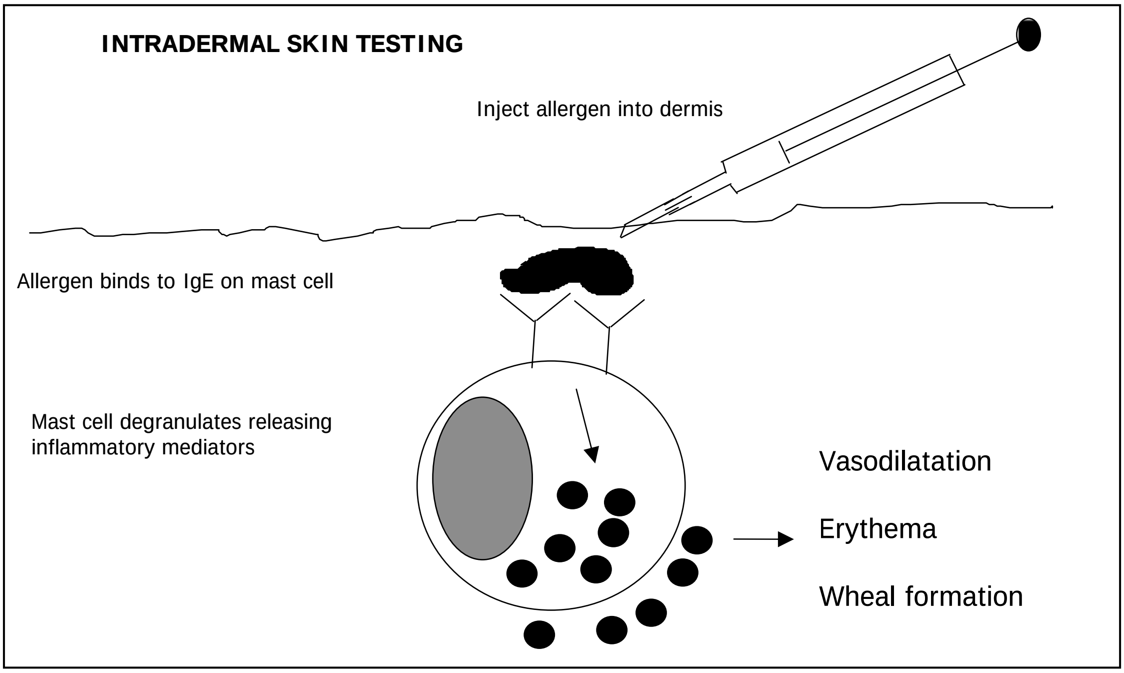
of antigens is similar to that used for intradermal skin testing, but there are usually fewer antigens tested than in a skin test.

3. If there is any IgE in the serum that is specific for a particular antigen, it binds to it. The bound IgE is then detected by adding an enzyme-linked reagent that can bind to IgE. This is either a monoclonal antibody or a receptor for IgE molecules.
4. A substrate is added that changes colour when it contacts the enzyme attached to the IgE reagent. The degree of colour change is proportional to the amount of IgE that is bound.
5. The colour change is measured by an automated reader and the results are reported as a numerical score. The significance of various scores is indicated by the laboratory.

Interpretation

The in-vitro test is interpreted by correlating the positive reactions with the patient's history. Clinically relevant reactions can then be used to choose allergens for specific immunotherapy.

Image 21.1. - A comparison of allergy testing methods for atopic dermatitis


INTRADERMAL SKIN TESTING
Inject allergen into dermis
Allergen binds to IgE on mast cell
Mast cell degranulates releasing inflammatory mediators
Vasodilatation
Erythema
Wheal formation

IN-VITRO MEASUREMENT OF ALLERGEN-SPECIFIC IgE

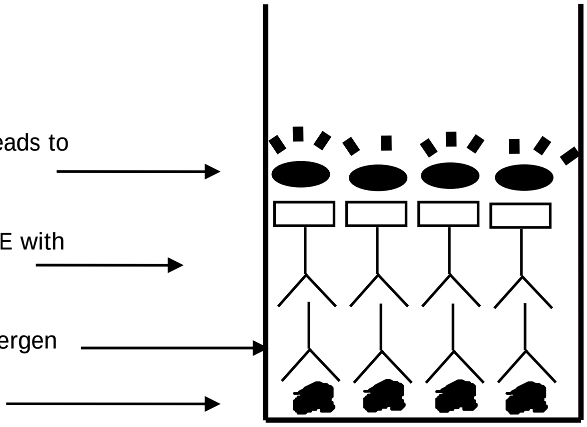
Step 5 – Colour change is measured by a plate reader that gives a numerical score.

Step 4 - Add substrate to detect bound antibodies (leads to colour change)

Step 3 - Add either anti-canine IgE or receptor for IgE with an enzyme connected to it

Step 2 - Add serum sample. Specific IgE binds to allergen

Step 1 - Coat ELISA plate with allergen



PREPARATION OF ANIMALS FOR ALLERGY TESTING

Before either of the above tests are performed, it is important that the patient is adequately prepared. Clinicians should ensure that:

- Other pruritic diseases have been ruled out.
- The skin is in a suitable condition for skin testing and is not covered in crusts or infection.
- Anti-pruritic drugs have been withdrawn for a suitable period of time.

Table 21.1. Approximate withdrawal times for anti-pruritic drugs before allergy testing (weeks). These times may vary for an individual dog or cat.

Treatment	Intradermal testing	In-vitro testing
Alternate day prednisolone	3	?
Daily prednisolone	4	?
Depo-Medrone injection	6-10	?
Topical steroids (inc. ear drops)	1	0
Antihistamines	1	0
Cyclosporine	?	0
Essential fatty acids	1	0

INTRADERMAL VERSUS IGE SEROLOGY - WHICH TEST IS BEST?

Veterinary dermatologists are often asked which of the above tests is the best. When answering this question, it is important to remember that the tests are not measuring the same thing. In-vitro tests merely measure the amount of allergen-specific IgE that is present in the blood. Intradermal skin testing detects the presence of allergen-specific IgE that is bound to mast cells in the skin. However, intradermal skin tests also measure mast cell releasability (this can be altered in atopic dermatitis) and the response of the skin to inflammatory mediators. Intradermal skin tests, therefore, provide a complete functional assessment of the all the pathways that are required to initiate an allergic reaction in the skin; in vitro tests only measure one particular point in the pathway. Skin tests also usually evaluate a larger range of allergens. For these reasons, most veterinary dermatologists regard intradermal skin testing as the superior test.

However, in my opinion, the best way to evaluate an atopic dog is to perform both skin testing and IgE serology at the same time (if finances allow). Experience has shown that positive results can be obtained in a skin test that are negative on blood tests, and vice versa. This may reflect different phases of the allergic pathway being detected at different times, but this hasn’t been proven.

If it is not possible for a dog or cat to undergo intradermal skin testing at all (e.g. if there is no local referral centre, the owner doesn’t want referral), in-vitro tests can be used as an alternative to identify allergens for use in immunotherapy. In some reports, the response to treatment is nearly as good with this approach as that obtained with intradermal skin testing. However, this success rate has only been reported when the test has been performed by dermatologists and, to date, has not been confirmed in properly controlled studies

The major stumbling block when this test is performed in general practice is the fact that the test can be positive in completely normal animals, or animals with other skin diseases. This has tripped up many an unsuspecting vet over the years and I have seen lots of cases coming through the dermatology clinic that have been diagnosed with atopic dermatitis on the basis of these tests that were actually suffering from demodicosis, scabies, flea allergy, Malassezia dermatitis, recurrent pyoderma, food allergy or contact allergy. You can imagine the client’s frustration when they are 12 months into allergen-specific immunotherapy, only to find that the original diagnosis was incorrect and that the previous years treatment was a waste of time and money.

I like to think of allergy tests as being the final piece of a jigsaw that can complete the diagnostic picture, but on their own they can only convey very limited information. Bearing in mind that the main reason for doing them is to allow allergen-specific immunotherapy (a long term treatment), the stakes are pretty high to get it right first time.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen immunotherapy (hyposensitisation or desensitisation) involves the subcutaneous injection of gradually increasing doses of relevant allergens over a period of time until a maintenance dose is reached. The treatment is thought to work by correcting the imbalance in the animal's T lymphocyte populations with the net effect that Interleukin-4 secretion is reduced. This reduces IgE synthesis and encourages IgG synthesis, which may be protective.

Formulation, Dosage Schedule and Route of Administration

Selection of the allergens to be included in the vaccine is based on the positive results obtained in the intradermal skin test and/or the in-vitro test. Some companies and dermatologists limit the number of allergens in a vaccine to ten. If more than ten allergens are thought to be significant, a second vaccine can be made up. Other dermatologists simply put all the relevant allergens into one vaccine. To date, there is no evidence that one method is superior to the other.

Allergen vaccines are either prepared in aqueous form or alum-precipitated form (which has a depot effect allowing less frequent injections). Vaccines prepared in Australia are of the aqueous type.

Aqueous vaccines are given according to an induction schedule (in which the dose and dosing interval is gradually increased) followed by a maintenance schedule. The induction course may comprise 2 or 3 different vials of different concentrations. I currently prescribe 2 vials, with vial 2 being ten times more concentrated than vial 1 (see Table 2).

Table 21.2. Injection schedule for aqueous allergens used by the author. This can differ slightly depending on the dermatologist.

	Volume	**Day**
Vial 1	0.1 cc	0
	0.2 cc	2
	0.4 cc	4
	0.6 cc	6
	0.8 cc	8
	1.0 cc	10
Vial 2	0.1 cc	12
	0.2 cc	14
	0.4 cc	16
	0.6 cc	18
	0.8 cc	20
	1.0 cc	22
	1.0 cc	+ 1 week
	1.0 cc	+ 1 week
	1.0 cc	+ 1 week
	1.0 cc	+ 2 weeks
	1.0 cc	+ 2 weeks
	1.0 cc	+ 2 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks
	1.0 cc	+ 3 weeks

Efficacy

Allergen immunotherapy takes 2 - 9 months before a beneficial effect is seen. The normal recommendation is that dogs receive the vaccine for at least a year before a final decision is made as to its efficacy. Therefore, during the early phase of allergen immunotherapy, it is usually necessary to use some additional therapy to control the clinical signs. In most studies published to date, similar success rates have been reported. 25% of atopic dogs can be controlled with immunotherapy alone. A further 50% show a beneficial response, but the dog requires some other form of non-steroidal therapy. The remaining 25% show no response at all. ***One study has demonstrated that immunotherapy is more successful if it is prescribed and monitored by a specialist dermatologist.*** The success rate of allergen immunotherapy in cats is suspected to be similar, but precise figures are not known. Owners need to be informed of the slow nature of this type of treatment and the likely success rates so that they don't have unrealistic expectations. If successful, allergen immunotherapy must be continued for the remainder of the animal's life in the vast majority of cases.

Adverse Effects

Serious adverse effects of allergen immunotherapy are exceedingly rare. Some dermatologists recommend that the first five injections of the course should be given under veterinary supervision and the animal should remain in the clinic for 30 minutes to monitor for any adverse reactions. I don't recommend this, but inform the owners to administer the injections at a time when their local veterinary practice is open in case there are any problems. Potential adverse effects and the recommended course of action are shown in Table 3. If no problems occur, further injections can be administered at home by the owner (following appropriate instruction).

Table 21.3. Adverse effects of allergen immunotherapy

Adverse effect	**Treatment**
Mild pruritus at the injection site	None
Generalised pruritus	Administer antihistamines for 2 days before the next injection
Generalised urticaria	Administer glucocorticoids by injection Administer antihistamines for 2 days before the next injection
Anaphylaxis (vomiting, diarrhoea, pale mucous membranes, respiratory distress, collapse)	Administer 0.01 ml/kg 1:1000 epinephrine IM or SC Monitor very carefully if the injection course is continued Provide owner with an EpiPen® (automatic epinephrine injector available from pharmacists)

What If The Treatment Fails?

Animals may fail to respond to allergen immunotherapy for the following reasons:

Reason for failure	Solution
Animal improves after each injection but relapses before the next one is due	Give injections more frequently
Animal improves initially but response seems to deteriorate as the course progresses	Check for concurrent problems. If none are present, reduce dose of injection by 50%. If still no improvement, reduce dose by a further 50%. If still no improvement, repeat food trials and consider further testing. If additional allergens are identified, modify vaccine prescription
Animal is doing well but becomes more pruritic after each injection	Reduce dose of injections by 50%
Animal completely fails to respond despite taking above measures	25 – 30% of dogs will fail to respond to allergen immunotherapy. Discontinue and resort to other therapies

ALTERNATIVE FORMS OF IMMUNOTHERAPY

There are a number of variations to the standard form of immunotherapy as described above. These will not be discussed in detail but include:

- Rush immunotherapy – a standard immunotherapy protocol but with the induction course compressed into a 24 hour period
- DNA adjuvanted immunotherapy – this involves the addition of immunostimulatory liposome-nucleic acid complexes to the allergen mix and was shown to improve the efficacy in a small pilot study
- Anti-IgE immunotherapy (Omalizumab, Xolair) – this reduces the levels of circulating IgE and can be efficacious in humans with asthma and IgE-mediated atopic dermatitis. Its use has not yet been reported in the veterinary literature.
- Interferon gamma immunotherapy – this is not allergen specific, but has been shown to have efficacy in the management of canine atopic dermatitis, presumably by reducing TH2 type cytokine responses.

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NOTES:

Chapter 22

Feline Allergic Skin Disease

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Our knowledge of feline allergic skin disease is rudimentary compared to what is known in the dog. In 2001, a Task Force comprising a number of Diplomates from the American College of Veterinary Dermatology reviewed the literature on canine atopic dermatitis and put together a document comprising twenty four review papers[1]. Such an endeavour would still be impossible in the cat due to the scarcity of publications on the subject.

The major categories of allergic skin disease that have been described in the cat are:

- Flea allergy dermatitis
- Atopic dermatitis
- Cutaneous adverse food reactions (food allergies)

CLINICAL APPEARANCE OF FELINE ALLERGIC SKIN DISEASE

Cats with allergic skin disease have a wider variety of clinical presentations than dogs [2, 3]. This clinical variability has led to the concept of feline cutaneous reaction patterns. Four main patterns are currently recognised:

- miliary dermatitis
- feline symmetrical alopecia
- the eosinophilic granuloma complex
- head and neck pruritus

These patterns are a common reaction of feline skin to a diverse range of diseases including:

- allergic skin disease (the most important group) - fleas, atopic disease, food allergy

- ectoparasite infestation - lice, *Otodectes cynotis, Cheyletiella* spp, *Trombicula* spp and *Demodex* spp.
- bacterial and fungal infections
- may also be idiopathic
- behavioural factors may be present in some cases

Miliary Dermatitis (Papulocrustous Dermatitis)

Characterised by miliary, papulocrustous lesions, most commonly over the dorsum, but lesions can be anywhere. Commonly associated with secondary alopecia. Most commonly caused by flea bite hypersensitivity.

Feline Symmetrical Alopecia

Characterised by bilaterally symmetrical alopecia with non inflamed skin. The remaining hair is usually stubbly. Most commonly affects the ventral abdomen, caudal hindlimbs and lateral abdomen. The dorsum is not usually affected. Most commonly caused by fleas or other hypersensitivities. However, psychogenic forms have been described in nervous breeds. It is critical when presented with this condition to ascertain whether the cat is licking the hair out, or whether it is falling out. Many owners will think the hair is falling out. In the vast majority of cases, it is being licked out. If there is any doubt, perform a trichogram (examine some plucked hairs under the microscope).

Eosinophilic Granuloma Complex

This complex comprises three conditions - the indolent ulcer, eosinophilic plaque and eosinophilic granuloma which may occur separately or in any combination with each other. Their aetiology is multifactorial but cutaneous hypersensitivity reactions to fleas, food and environmental allergens (atopic disease) appear to play the most significant role. The conditions are quite distinctive but cytology can be used to confirm the clinical diagnosis.

1. Indolent ulcer: These are well demarcated, alopecic, reddish-brown ulcers with raised borders. They usually occur unilaterally or bilaterally on the upper lips. Pruritus is not usually observed by the owner.

2. Eosinophilic plaque: These are well demarcated, alopecic, raised plaques with a moist, red surface which may be eroded or ulcerated. They are usually located on the ventral abdomen, thorax and medial aspect of the hind legs but may occur anywhere. They are extremely pruritic. A circulating eosinophilia is often present. Cytology of impression smears reveals large numbers of eosinophils.
3. Eosinophilic (linear) granuloma: These are well-defined, firm, raised, yellow to pink, lesions that usually occur on the caudal aspect of the hindlimbs or in the oral cavity but may occur elsewhere. Oral lesions may cause drooling and dysphagia. They are usually pruritic although this may not always be observed. A circulating eosinophilia is occasionally present and there may be local lymphadenopathy.

Head and Neck Pruritus

Characterised by severe scratching around the head and neck. Usually see alopecia, excoriations and sometimes ulceration. There are often severe lesions on the cheeks. It has been suggested that pruritus restricted to the back of the neck may also be due to herpes virus infection of nerve endings following vaccination.

Combination Patterns

Some cats present with more than one of the above patterns at the same time.

Generalised Pruritus

Some itchy cats present with obvious pruritus but without falling into one of the above categories. Despite this, the differential diagnoses remain the same.

Feline Mosquito Bite Hypersensitivity

This seasonal disease tends to affect the face and pinnae of cats. Lesions often occur on the dorsal muzzle and may appear rapidly. Mild forms may have papules, crusted papules and alopecia. More severe forms show a well demarcated patch of swelling, erosion, ulceration and exudation. On the pinnae, multiple papules may be seen, similar to military dermatitis. Major differential diagnoses are feline herpes virus infection, pemphigus foliaceus and squamous cell carcinoma. Cytology and biopsy can be used if differentiation is required. On biopsy, there is a marked eosinophilic infiltration into the dermis and hair follicle walls, often with overlying ulceration.

Lesions are known to occur at the sites of mosquito bites and resolve if cats are kept strictly confined indoors. Treatment with glucocorticoids may hasten resolution and control signs if indoor confinement is not possible.

Urticaria Pigmentosa

In humans, this is a form of mast cell neoplasia. However, in cats, it is common to see lots of mast cells in biopsies from allergic skin disease. In most cases, this merely reflects a mild increase in the numbers of mast cells that are normally there. In Rex breeds, however, there can be extremely high numbers of mast cells (>50 per high power field). Such a density of mast cells is sometime referred to as urticaria pigmentosa, although it is almost certainly a different entity to what occurs in people. It appears to reflect either an extreme mast cell response to an allergic stimulus (food allergy, atopic dermatitis) or a genetically determined dysregulation in mast cell proliferation. The syndrome in cats is typified by extreme pruritus, especially of the ventrum. Multiple erythematous papules and plaques can be seen in affected areas.

Feline Hypereosinophilic Syndrome

Feline hypereosinophilic syndrome is a rare multi-systemic disease that affects multiple organs as well as the skin. A marked infiltration of mature eosinophils occurs most commonly in the bone marrow, liver, spleen, lymph nodes and gastrointestinal tract, but the heart, skeletal muscles and skin can also be involved. If the skin is affected, lesions can be generalised and include erythema, papules, wheals and oedema. Cats with skin disease are usually highly pruritic. The diffuse eosinophilic infiltration can be documented on biopsy, but needs to be differentiated from other feline eosinophilic skin diseases. The prognosis for this condition is poor and successful treatment outcomes have not been reported.

DIAGNOSIS AND MANAGEMENT

Flea Allergy Dermatitis

Flea allergy dermatitis has been well characterised and usually poses no diagnostic difficulties if evidence of fleas can be found. The main problem is to rule out the role of fleas in free range cats before embarking on more elaborate investigations for food allergy or atopic dermatitis. In most cases, the only practical option is to institute very tight flea control measures first to see if there is a resolution [4-9]. This may entail keeping the cat inside for a trial period to prevent exposure to outdoor sources of fleas.

Feline Atopic Dermatitis

In the Task Force document, canine atopic dermatitis was defined as a genetically-predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, associated most commonly with IgE antibodies to environmental allergens[1]. This definition is important because it encompasses most of the parameters that are used for diagnosis and management of this condition in dogs. For example:

- Genetic predisposition – accounts for the historical features of early age of onset and predisposed breeds
- Inflammatory and pruritic allergic skin disease with characteristic clinical features – accounts for the distinctive clinical phenotype (lesion types and distribution) seen on physical examination that is a major component of the diagnosis
- Commonly associated with IgE antibodies to environmental allergens – this forms the basis of intradermal allergy testing and IgE serology. These tests can be used to support a diagnosis of IgE mediated atopic dermatitis and allow formulation of immunotherapy vaccines.

What evidence is there for the existence of a similar feline disease, and could such a definition be applied to the cat?

Genetic Predisposition

Apart from one publication that described a pruritic skin disease in three littermates that responded to allergen-specific immunotherapy [10], there is no convincing evidence for a genetic predisposition to atopic disease in the cat. No breeds of cat are predisposed to the disease and no lines of atopic cats have been described to date.

Inflammatory and Pruritic Allergic Skin Disease with Characteristic Clinical Features

Unlike the dog, there is, as yet, no defined phenotype for what an atopic cat should look like. Without a characteristic clinical appearance, it is difficult to establish any useful clinical criteria that might point to a diagnosis of feline atopic dermatitis. Cats with presumed atopic disease can present with any of the four cutaneous reaction patterns [2, 3, 11]. To date, there is no evidence that one pattern is more likely to represent atopic disease than any other.

Role of IgE Antibodies and Environmental Allergens

The development of IgE antibodies to environmental allergens is regarded as a pivotal mechanism in the pathogenesis of atopic dermatitis in dogs. Numerous studies have demonstrated that allergen specific IgE concentrations are elevated in atopic dogs with house dust mites being the most commonly implicated allergens. Evidence that cats have a reaginic antibody (IgE) was first reported in cats with *Otodectes cynotis* infestation [12]. Subsequently, DeBoer provided three lines of evidence that feline IgE existed [13]. First, a molecule from feline serum was detected on gel electrophoresis that had the same molecular weight profile as canine IgE. This molecule could be removed from feline serum by passing it through a column to which an anti-canine IgE reagent had been attached. Secondly, the anti-canine IgE reagent was able to cause mast cell degranulation in an in vitro feline bladder contraction model of allergic reactions. Thirdly, anti-canine IgE reagents were able to induce wheal formation when injected into cat skin (reverse cutaneous anaphylaxis). More recent studies have used molecular techniques to demonstrate that cats have an immunoglobulin molecule with similar identity to canine IgE [14]. Taken together, these studies provide strong evidence that feline IgE exists. Attempts to measure the levels of feline IgE in serum have required the production of reagents able to detect feline IgE directly. This has been achieved in three ways, namely polyclonal antibodies [15], monoclonal antibodies [16] and the human FcεR1 receptor that is used to measure IgE levels in dogs and humans [17]. Unfortunately, studies using these reagents in cats have shown no difference in concentrations of house dust mite specific IgE in cats without skin disease and cats with presumed atopic skin disease. Hence, although feline IgE exists, there is currently no evidence that it is involved in the skin diseases that we currently label as feline atopic dermatitis.

Diagnosis

Due to the difficulties in establishing precise historical, clinical and immunological features of feline atopic dermatitis, the diagnosis remains a challenge. Histopathology does not provide further specific information that differentiates the various allergic diseases. Biopsies from cases of putative feline atopic disease were shown to contain $CD4^+$ lymphocytes and mast cells in non-inflamed areas, whereas eosinophils are more prominent in lesional skin and eosinophilic granuloma lesions [18-21]. However, these features would not distinguish between flea allergy, food intolerance or atopic dermatitis. Essentially, the condition should be regarded as a diagnosis of exclusion, once the role of parasites (especially fleas) and food intolerance have been ruled out. Despite the uncertainty surrounding the role of IgE in feline atopic disease, dermatologists still frequently measure levels of mast cell bound IgE by intradermal testing or serum levels by serology once the "clinical" diagnosis has been established by rule-out. Intradermal testing can be unrewarding in cats and far more difficult to interpret than in dogs. The formation of erythematous wheals, even at the positive control site, is much less common than in dogs, although obvious positive reactions are sometimes obtained. Some dermatologists inject fluorescein prior to performing the test to allow reactions to be seen under UV light[22]. Although positive reactions are commonly obtained using IgE serology, their precise significance is not known as highlighted above.

Management

Paradoxically, the use of allergen-specific immunotherapy based on intradermal or serological allergy tests can be successful in ameliorating the symptoms of feline atopic skin disease, although reports in the literature relate to open and poorly controlled studies [23, 24]. A rush protocol has recently been described in a pilot study [25]. The mode of action of such therapy in cats is not known and it isn't even clear if it is acting in an allergen specific way or not. Hence, at this stage, it would still be fair to say that the efficacy of this treatment in cats hasn't been proven.

In many cats, anti-inflammatory medication is required to control the signs of presumed atopic disease. Glucocorticoids are usually well tolerated and still represent the symptomatic treatment of choice [2, 3, 11].

Antihistamines have been reported to be effective in a number of cats with atopic dermatitis [3, 26]. Chlorpheniramine is most commonly used although the author has had some success with cetirizine in lesions of the eosinophilic granuloma complex.

The use of cyclosporine is the most recent development in the management of canine and feline atopic dermatitis [27-34]. As in dogs, similar efficacy to prednisolone has been demonstrated[35]. The development or recrudescence of latent toxoplasmosis is a current concern [36, 37].

Food Allergy (Cutaneous Adverse Food Reaction)

There are currently no specific dermatological features that distinguish an atopic cat from a cat suffering from adverse food reactions. All four of the cutaneous reaction patterns may be observed. The presence of predominantly facial lesions has often been considered suggestive of dietary allergy [38-40] and the presence of concurrent gastrointestinal signs can be a diagnostic clue. Fish, lamb and dairy products have commonly been incriminated in cases of feline food intolerance.

Pathogenesis

No immunological studies have been reported that elucidate any of the mechanisms that might be involved in cutaneous food allergies in cats.

Diagnosis

There are many pitfalls when undertaking diet trials in dogs and cats. These have been extensively reviewed [41] and will not be repeated here. In the past, most dermatologists recommended home cooked diets to investigate potential food intolerances [41]. However, more recently, especially with the introduction of hydrolysed diets, food trials using commercial diets have become more popular. The successful use of such diets has recently been reported in dogs [42]. The major advantages of commercial diets are that they are nutritionally balanced and improve owner compliance. The length of required diet trials is still controversial. In a study reporting food intolerance in 13 cats, Rosser indicated that up to 10 weeks may be necessary before clinical signs abate [43]. This finding has not been corroborated in other studies and it is still not known if this is a repeatable result. The principle of the dietary investigation has always been to feed an elimination diet to see if the animal improves, and then to challenge the diet to see if the condition relapses. In the reported literature, this would be considered diagnostic for food allergies. The author adopts a more rigorous approach which requires the above cycle to be repeated, and then to either identify specific ingredients that can trigger a reaction, or to achieve long term control of the condition with diet alone. Due to these more stringent criteria, food intolerance is a rare diagnosis in the author’s clinic.

Management

The only effective way of managing genuine cases of food intolerance is to avoid the foodstuffs that are involved. Long term feeding of commercially available limited ingredient or hydrolysed diets are the most appropriate option. Glucocorticoids may have to be used in some cases if dietary manipulation is not possible. Such therapy may also be required if a cat suffers from combination allergy.

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Chapter 23

Interactive Case Sessions: The Pruritic & Atopic Patients

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Chapter 24

Skin Biopsy: How, Why, Where and Interpreting the Results – Part 1

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INTRODUCTION

Skin biopsy and histopathology is a powerful dermatological diagnostic tool but its success relies on teamwork between clinician (for case and lesion selection, sample procurement, specimen preservation, supply of appropriate history, and interpretation of results in light of the case) and pathologist (for sample processing, and examination and interpretation of the sample in light of supplied history). Without this teamwork, results can be disappointing to clients, clinicians and pathologists.

WHY DO WE BIOPSY?

In general, skin biopsy is performed to confirm a clinically suspected diagnosis within the skin that cannot be confirmed with less invasive techniques (such as skin scrapings, cytology, and trichograms). Biopsies are typically submitted for subsequent histopathological analysis, but in some cases other specific tests on skin biopsy specimens may be required for confirmation of a diagnosis including:

- polymerase chain reaction (PCR) for a variety of infectious organisms
- bacterial and/or fungal culture
- viral isolation
- electron microscopy.

Biopsy can also be useful in cases where a diagnosis cannot be confirmed, by narrowing a possible differential list, and because cellular changes may provide a guide to therapy even in cases where a definitive diagnosis remains elusive.

Specifically, there are several additional situations where biopsy & histopathology should be considered:

- **To diagnose skin tumours, or remove tumours and check the margins if neoplastic**

  As both the type of tumour and the completeness of excision may have profound impact on the patient's prognosis, histopathology should be mandatory on all excised tumours.

- **When it is required to confirm a diagnosis prior to commencing treatment (especially where treatment is expensive or potentially dangerous)**

  The skin has only a limited number of ways of reacting to disease processes, and unfortunately many of these can look similar. To further complicate things, the appropriate treatment of similar appearing diseases may be markedly different to the point of contraindication e.g. pemphigus foliaceous and *Trichophyton* dermatophytosis.

- **Persistent ulceration**

  While ulcers are often unrewarding biopsies, if persistent ulcers are the only lesions present then biopsy of these are more likely to be rewarding.

- **Where an otherwise straightforward case is not responding to therapy**

  While this is listed as a biopsy indication in several texts, the authors are not so sure. A failure of an apparently straightforward case to respond to therapy may be a therapeutic failure, not necessarily a diagnostic failure, and in that instance biopsy will be unrewarding. Furthermore, if there has been a diagnostic failure, then biopsy is not necessarily the right diagnostic step to get further answers. The authors would recommend a second opinion (via telephone consultation or referral) prior to recommending biopsy and histopathology in these cases.

- **Vesicular diseases**

  Diseases causing vesicles almost always require biopsy to confirm the diagnosis.

- **Serious dermatosis**

  Any serious, potentially life threatening dermatosis may require rapid diagnosis. While biopsy may or may not be the diagnostic tool of choice in these cases, the urgency of the case may dictate that more aggressive diagnostics are performed sooner.

LIMITATIONS OF BIOPSIES

Biopsies are not a perfect diagnostic tool. They may be unrewarding because they have been done late in the disease process with significant non-specific changes overshadowing primary disease changes, because of poor specimen collection or poor biopsy technique. Biopsies also tend to be unrewarding in pruritic cases with few primary skin lesions - the diagnosis in these cases is often the result of a clinical workup (though there are occasional exceptions).

Lastly, even in ideal circumstances, biopsy may be less useful than expected, and in the worst scenario misleading, in cases where the clinician fails to match the biopsy results with the clinical presentation. A biopsy and the tests subsequently performed upon it add to the information database, but do not replace a good history, physical examination and other clinical tests. A definitive diagnosis is made by the clinician in charge of the case, not the pathologist, and it should always be the result of a correlation of clinical findings and test results (or a ‘clinicohistopathological correlation’). This is explained more in part 2.

WHEN DO WE BIOPSY? TIMING IS EVERYTHING

When Concurrent Disease is Controlled

Skin diseases do not exist in a vacuum and secondary infection is a common complicating problem. Both bacterial and yeast toxins and the immunological response of the host to these organisms, can alter the histological appearance of the biopsy specimens making the pathologist’s job difficult. There are some clinical situations also where infections may mimic other diseases (such as mucocutaneous pyoderma and nasal lupoid dermatosis aka DLE). If there is any doubt over the possible presence of infection, i.e. if the skin shows any crusting, scaling, papules or pustules or any pruritus, then antibiotics (e.g. cephalexin 22mg/kg bid) must be given for at least 2-3 weeks prior to biopsy. If there is good improvement then antibiotics should continue until 7-10 days after the point of maximum improvement before considering biopsy.

The take home message then is that where possible it is best to diagnose and clear infections PRIOR to taking a biopsy. The exception to this rule is where a primary infection is suspected and biopsy is being taken for deep tissue culture.

When Primary Lesions are Present

Primary lesions are those produced by the disease alone and can include pustules, vesicles, papules, erythema and macules, purpura, nodules, verrucosities (well defined hyperkeratosis), some alopecia, crusts, atrophy, sclerosis (scarring) and comedoes (‘blackheads’). They are the lesions most likely to give clear cut histopathological changes, and thus the lesions most likely to give a definitive diagnosis.

Secondary lesions are not produced by the primary disease and may be caused by trauma or aging of the primary lesions. These include excoriations, most ulcers and erosions, most sclerotic lesions, lichenification, some crusts, comedoes and alopecia. Secondary lesions are often not diagnostic, though there are exceptions.

In some cases, primary lesions (esp. vesicles and pustules) can be very fragile and thus transient, and may not be present at all times. It may be necessary in some cases to admit these patients for the day and re-examine the skin every 2-3 hours for the presence of these short-lived but valuable lesions for immediate biopsy if they have been identified previously.

When Off Glucocorticoids

Topical and systemic glucocorticoids can significantly alter histopathological changes in the skin including follicular telogenisation, atrophy of the dermis and adnexal glands, and a reduction in inflammation. The latter is especially important as the type and distribution of inflammation can be the key to achieving a diagnosis. Minimum withdrawal times that have been recommended include 2-3 weeks for oral and topical medications, and 6-8 weeks for injectable depot preparations.

However, a more practical guide is simply to withdraw glucocorticoids long enough for primary skin lesions to return for biopsy. This requires close contact with the client regarding progress (often deterioration in the pet's skin) and sometimes multiple re-examination to see if appropriate lesions are present for biopsy. This approach should minimise pet discomfort while maximising the chance of a diagnostic biopsy. Good client communications are essential in this period because they may rightly perceive worsening of the skin and no treatment being instituted. Without this approach though, there is a serious risk that any biopsies taken will be worthless.

Ironically, glucocorticoids may make some infections and mite infestations worse, allowing an easier histopathological or culture diagnosis. This practice is not recommended because of the risk of significant disease worsening.

WHERE DO WE BIOPSY? PRINCIPLES OF BIOPSY SITE SELECTION.

Site selection is partly an art. Experienced clinicians will pick lesions that they suspect will show diagnostic changes. Consciously or subconsciously, this is a result of understanding the pathophysiology of the differential diagnoses and the changes they produce in the skin. While biopsy of specific types of lesions is dealt with is the second part of these notes, there are several general principles that will help guide site selection to maximise the usefulness of the specimens submitted:

- **Aim for primary lesions** (See above for details.)
- **Early lesions are often the best, containing the most diagnostic changes**

  However, some severely affected lesions can also be useful, so long as they are not secondary lesions. An example of this is some alopecic lesions.
- **Most of the time ulcers and draining sinuses are useless**

  Ulcers lack epidermis totally (meaning that if diagnostic changes are epidermal there is no chance of making the diagnosis) and both ulcers and sinuses cause very significant inflammatory changes in the superficial dermis that can mask other processes. Exceptions to the rule include some deep dermal diseases (such as large vessel vasculitis), an occasional deep infection (though intact lesions are better), where persistent ulcers are the reason for biopsy or some squamous cell carcinomas. If ulcers are to be biopsied then make sure both a border region from normal to affected skin is included, as is tissue very deep to the ulcer as these may contain diagnostic clues.
- **Some grossly normal skin is never a bad thing to get**

  It allows the pathologist to compare it with the diseased skin and this can help with the detection of subtle changes.
- **Consider a second opinion in difficult cases**

  Where the presentation is unusual, disease process unknown and precluding meaningful differential diagnosis list formation and rational lesion selection, consider a dermatological referral or a phone consultation with accompanying digital images to aid in case workup and biopsy site selection.

- **If in doubt, biopsy all lesion variants**

  Where the presentation is unusual, disease process unknown and precluding meaningful differential diagnosis list formation and rational lesion selection, and a dermatologist is not available, biopsy the full spectrum of lesions from mild to severe. Less dramatic lesions may have more diagnostic information. Submission of large numbers of biopsies, while maximising the chance of diagnosis, may incur a significant additional cost burden, depending on the laboratory.

Avoiding Artefacts

Garbage in = Garbage out. Pathologists cannot successfully interpret specimens where artefacts distort the histological picture.

Artefacts resulting from improper site selection include biopsies showing excoriation, maceration, ulceration, or necrosis. Topical medications may also causing staining abnormalities.

HOW DO WE BIOPSY? GENERAL BIOPSY TECHNIQUES

Preoperative Preparation

The main preoperative considerations in most cases are to:

- Establish a differential diagnosis list.
- Rule out as many differentials as is possible with in-house testing (skin scrapes, trichograms, cytology)
- Ensure secondary infection is cleared.
- Stop glucocorticoids if possible.
- Ensure the appropriate fixative or transport medium is available. If necessary, discus these requirements with the laboratory prior to biopsy. There is nothing worse than finding out the clinic is out of formalin as the first biopsy is removed!
- Know what lesions you are aiming to biopsy before you start.
- Mark each biopsy site with a permanent marker so as to be able to locate it again following anaesthesia. The authors typically use 4 dots around the lesion.

Anaesthesia

Anaesthesia may be a general anaesthetic (GA; either injectable and/or gaseous), or depending on the site, sedation (e.g. Domitor) with local anaesthesia may be appropriate. General anaesthesia is generally recommended for facial, nasal, pinnal or paw biopsies. Most other sites can be biopsied under sedation and local anaesthesia.

The most commonly used local anaesthetics in small animal practice are lignocaine (lidocaine) and prilocaine. Prilocaine is similar to lignocaine but of lower toxicity.

The authors use 2% prilocaine diluted 50:50 with saline with 0.5-1ml injected deep SC under the marked punch biopsy site. Depending on dose, tissues and the anaesthetic, onset of local anaesthesia is typically 5-10 minutes (be patient!), and lasts 45-120 minutes (longer if a preparation containing adrenalin is used).

Local anaesthetics can on occasion cause toxicity, with most toxicity a consequence of unintended intravenous administration. Adverse effects are usually dose related. For lignocaine these include CNS effects (including muscle tremors, recumbancy, anxiety, seizures, blindness and extensor rigidity), GIT effects (including nausea and vomiting, usually transient) and cardiac effects (including bradycardia, decreased cardiac output and blood pressure). These effects may be seen using lignocaine 2% at 1ml/kg SC in sheep and 0.5ml/kg SC in cats. 0.5ml SC in the head of a small dog or puppy has been reported to cause seizures.

Prilocaine has fewer of these toxic effects but methaemaglobinuria has been reported as a toxic side effect in humans. This effect was not reported at 0.2ml/kg SC of 2% prilocaine in humans. At the authors’ practice the total dose of prilocaine is usually limited to 0.2ml/kg of 1% diluted prilocaine. This leaves a reasonable margin for safety.

There are a few other limitations of local anaesthesia the clinician should be aware of. For biopsies of fat or subcutaneous tissue, a SC injected local anaesthetic can distort the tissues. Also, where biopsies are being taken for a deep tissue culture, it should be noted that lignocaine, bicarbonate (used as a buffer) and adrenaline can each inhibit various Gram-positive bacteria, Gram-negative bacteria, mycobacteria and fungi. In these cases, a ring block or GA is more appropriate.

Avoiding Artefacts

Intradermal (rather than subcutaneous) local anaesthesia can lead to collagen separation, pseudooedema and pseudosinuses.

Preparation

Biopsies for histopathology are generally non-sterile affairs. Standard surgical preparation can disrupt crusts and cause epidermal changes that can affect interpretation of the biopsy. In most cases then, a careful light hair clip is appropriate to avoid gross wound contamination and hair in the sutures. **Avoid clipping off crusts!** Scissors may be useful for cutting hair if there is ANY danger of touching the lesion. Some dilute 0.05% chlorhexidine may be used to clean the wound AFTER suturing has been performed.

Surgical preparations may be appropriate where pannicular biopsies are to be taken (so epidermal artefact is not important) or for deep tissue cultures (see later).

Avoiding Artefacts

Improper surgical site preparation can lead to inflammation, staining abnormalities and removal of superficial epidermal changes from surgical scrubbing and use of antiseptics.

Surgical Biopsy Technique

With skin biopsies, it is best to get as big a sample as is possible and as many samples as possible to maximise the chance of diagnosis. The authors tend to use 4-8mm punches depending on the location. Use of biopsy punches is appropriate for most skin biopsies, and tends to minimise trauma and the time of surgery.

Following anaesthesia, the biopsy punch is held perpendicular (at 90 degrees) to the skin over the lesion. The lesion of interest should be in the middle of the area to be biopsied, as this maximises the chance of it being cut into the section at processing. If there is a regional lesion, then getting all the same lesion in the punch area will remove the possibility of the lesion being missed in sectioning. Once lined up, even pressure is applied while simultaneously rotating the biopsy punch. The punch is always rotated in the same direction to avoid squashing the biopsy. After the biopsy has 'popped' through the skin, it may be possible to free the biopsy by angling the punch closer to the skin and continuing to rotate and gently applying pressure ('driller' technique). If this is not possible, then curved iris scissors can be slid down the side of the punch in the skin to cut off the sample at the panniculus.

It is important to minimise trauma to the sample with cutting and picking up so as not to cause artefacts, which may make interpretation harder after processing. The 'driller' technique is ideal as it avoids cutting and double handling. If this is not successful or possible, then the best thing to do is to use fine instruments and in most cases, pick the biopsy up by the panniculus. However, the clinician needs to consider where the lesion is within the skin, as there are certain diseases where an intact panniculus is required for examination. Thus for most of these deep diseases, picking the biopsy up by the epidermis may be satisfactory.

Excision biopsy with a scalpel should be considered for larger lesions, fragile lesions (vesicles, bullae, pustules), lesions where orientation of sectioning is paramount (as sectioning will be performed typically longitudinally in an elliptical biopsy) and deep fat. For deep fat biopsies, a second punch biopsy through the first punch biopsy hole to collect deeper tissue may also be appropriate.

The sample should then be blotted gently to avoid erythrocyte artefact before being placed in formalin or the transport medium. Closure of the wound can be done using simple interrupted sutures. This may take a little longer, but in the authors' hands at least look better and often have better apposition of the wound edges.

Avoiding Artefacts

A dull punch or poor technique can result in pseudovesicles or pseudoclefts shearing. Squeeze artefacts from forceps include pseudopapillomas, pseudonodules, pseudosclerosis, pseudosinuses, pseudocysts, and lobules of sebaceous glands within hair follicles and/or the skin surface. Use of electrosurgery for sample collection can result in dehydration, elongation and polarization of cells. Lastly, friction on the biopsy can cause intercellular oedema, clefts, and vesicles.

Biopsy Storage for Transport

For histopathology, it is important to put the biopsy sample in fixative quickly because autolysis starts immediately with removal. Formalin is used to preserve most biopsies (for routine staining) after they have been collected. Punch biopsies left under a hot surgery light can have microscopically observable damage in less than 5 minutes! Additionally, larger specimens (greater than 1cm) may require additional cuts to be placed in the sample to allow complete fixing. Larger specimens may also curl as a consequence of shrinkage in the fixative. Placing samples SC side down on tongue depressors or cardboard prior to placement in the fixative can minimise this.

For histopathology samples to be transported by post, samples should be soaked for 24 hours in fixative, then excess fixative drained out and the samples placed in a fixative-soaked gauze swab in a yellow top container for transport. The specific transport requirements will be available from your laboratory.

Different lesions from the same animal (and normal skin) should be placed in separate formalin pots and clearly labeled as to lesion and site of collection. This facilitates correlation with specific lesions identified at physical examination, and is essential where more than one disease is present on the one patient. One author has a boxer with five masses with five different histopathological diagnoses! In this case where one may have been malignant, it would have been imperative to be able to identify the location of that lesion. This would be nearly impossible if all lesions were submitted in the same pot.

Tissue samples not used for routine histopathology may have different storage requirements. Saline soaked swabs in sterile yellow topped specimen containers are used for deep culture samples. Samples for PCR can be submitted fresh or in saline and should be submitted quickly. Some samples for immunohistochemistry are better submitted as fresh frozen tissue, and samples for electron microscopy may require alcohol or freezing in liquid nitrogen. These requirements should be discussed with the laboratory prior to biopsy, and are another good reason for an accurate differential list prior to biopsy.

Avoiding Artefacts

Potential problems at the fixation stage include autolysis, failure to splint large samples resulting in curl artefact and shrinkage, accidental freezing of samples, use of nonbuffered formalin and excess alcohol in the fixative.

During processing, there may also be potential opportunity for artefact development that is out of the hands of the clinician, including inadequate dehydration in tissue processing, poor orientation of the specimen and cutting sections from dermis to epidermis.

Filling in the Request Form

Aside from the specific processing notes below, the key with filling in the request form is to include a concise history and physical description of the lesions, and your clinical differential diagnoses. In these modern times, submission of digital photos of lesions is also useful. While this does take a little time on behalf of the clinician it makes a world of difference to the pathologist who does not have the benefit of the patient immediately in front of them. It is a myth that ‘a good pathologist doesn’t need a history’ - if the clinician fails to give a good history the pathologist is working with one hand tied and the subsequent report will suffer.

Why is this? The skin has some limitations in how it responds to a disease, and not all skin diseases are histopathologically distinct. Providing clinical information increases the likelihood of getting useful information from the biopsy. Furthermore, if the sample is not representative of the entire disease process, then a good history may help alert the pathologist that what they are seeing is not correlating well with the history. Remember that pathologists are not clinicians or dermatologists. They are not extensively trained in the clinical aspects or management of disease. You, as the clinician, must take responsibility for the clinical interpretation of the histopathology report. Where the pathologist’s diagnosis does not fit with your differential diagnosis or where the diagnosis is a disease that you are not familiar with, then seeking the advice of a dermatologist would be recommended prior to commencement of treatment.

Other Possible Patient Complications

- Care should be taken with patients with possible bleeding disorders, or on aspirin or other anticoagulants. Where possible, these should be stopped 1-2 weeks before the biopsy.
- Problems should be anticipated with healing with severe metabolic diseases, collagen defects, patients on large doses of glucocorticoids or antimitotic drugs. Clients should be informed of this and sutures should be left in for a longer period of time.
- Infection is always a risk with non-sterile surgery. In practice though this is a rare complication in most patients. Use of perioperative antibiotics may be useful to minimise this risk.
- Biopsy of mast cell tumours (MCTs) can lead to release of vasoactive amines, heparin and other enzymes resulting in prolonged bleeding times post surgically and less likely, anaphylactic reactions. Where MCTs are on the differential diagnosis list, consideration should be given to using injectable antihistamines (e.g. chlorpheniramine maleate 0.5mg/kg SC/IM) as part of the premedication to reduce this risk.

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Chapter 25

Skin Biopsy: How, Why, Where and Interpreting the Results – Part 2

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SPECIFIC BIOPSY TECHNIQUES

Even in the absence of a specific diagnosis or differential diagnosis, knowledge of the basic pathophysiology of different types of lesions can assist with biopsy selection, and as a result, improve diagnosis.

Alopecic Lesions

Basic pathogenesis: Alopecic lesions occur grossly because of hair loss. Hair may be lost because of

- self trauma (e.g. allergies)
- environmental trauma (e.g. the cat that wears away hair over its scapulae getting under the fence)
- follicular infection (e.g. *Staphylococcus*, *Demodex*)
- follicular inflammation (e.g. alopecia areata)
- adnexal gland inflammation (e.g. sebaceous adenitis)
- neoplastic infiltration of the follicle (e.g. epitheliotrophic T-cell lymphoma)
- follicular cycle arrest (e.g. endocrinopathies)
- anagen defluxion (e.g. following a fever)
- follicular dysplasia (e.g. colour mutant alopecia)
- nutritional deficiency (e.g. EFA or protein deficiency)
- failure of follicular blood supply (e.g. vasculitis)
- follicular miniaturisation (e.g. pattern baldness)
- scarring.

Technique: The aim with biopsy of alopecic lesions is to try and get as many follicles in the biopsy as possible to maximise the chance of diagnostic changes being observed by the pathologist. 8mm punches are recommended and biopsies should be taken from the:

- most severely affected skin
- mildly affected skin
- normal skin
- skin with any abnormal hair colouration (if this is thought to be part of the disease process).

Ideally also, a line should be drawn parallel to the lie of the hair with a barrow permanent marker pen prior to biopsy. At the lab, the histopathology technicians will section along this line and this should give the pathologist the entire length of the longitudinally sectioned follicles to see, which maximises the chance of a diagnosis in most cases.

A cross section has more follicular units present, which can be useful for detection of some infections (e.g. dermatophytosis), but because the full follicle cannot be visualised, some diagnoses with very localised inflammatory changes (e.g. alopecia areata) may be missed. For a cross section to be made, a line should be marked across the lie of the hair.

Request Form Tips:

- *place the different lesions and normal skin in different pots and label them appropriately*
- *make a note to the scientists at the lab to 'Section along marked lines' if these have been marked*

Crusty Lesions

Basic Pathophysiology: Crusts may be serous, keratinous, inflammatory, haemorrhagic or a combination of these. Crusts are often secondary lesions and not diagnostic. However, in some diseases crusts may be very useful (e.g. dermatophilosus, and some dermatophytes and pemphigus foliaceous cases).

Technique: In these cases, it is important when biopsying to go right through the crust into skin and attempt to get the lesion out intact, and to ensure the crust is included in processing. Large biopsy punches (8mm) are again ideal where feasible, though with crusted nasal lesions this may not be feasible.

Request Form Tips:

- *It is important to write on the request form 'Please cut in crusts', otherwise the crusts may float off in the formalin and, following processing of the skin fragment, be thrown out with the formalin!*

Depigmented Lesions

Basic Pathophysiology: Melanocytes are present in the basal layer of the epidermis and in the bulb of active hair follicles. They transfer pigment to keratinocytes in the basal layer and hair shafts via long dendrites. Pigment loss may occur because of :

- loss of melanocytes (e.g. vitiligo, toxic effects of some chemicals in rubbers and plastics)
- congenital pigmentation disorders (e.g. Chediak-Higashi syndrome)
- lack of melanin precursors (e.g. copper deficiency)
- disruption of melanin transfer because of significant epidermal infiltrate (e.g. epitheliotrophic lymphoma, mucocutaneous pyoderma, pemphigus foliaceous)
- diseases causing hydropic degeneration of basal cells (e.g. cutaneous lupus)

Technique: The key with depigmenting lesions (e.g. mycosis fungoides, nasal lupoid dermatosis) is to try and biopsy the grey lesions as these are the lesions that are actively depigmenting and are most likely to contain diagnostic changes. Ensure that the punch contains ONLY grey skin so as not to lose diagnostic changes with sectioning. If no grey lesions are present then an elliptical biopsy across the border region between pigmented and depigmented skin is best to ensure the 'active' region is sectioned in at the lab.

Pustules / Vesicles

Basic Pathophysiology: Pustules ('pimples') and vesicles ('blisters') are critical primary lesions in some diseases.

Pustules are aggregations of inflammatory cells, typically neutrophils, in the epidermis. They may or may not be associated with follicles. Follicular pustules are often associated with causes of folliculitis bacterial infections, demodicosis or dermatophytosis.

Non-follicular pustules may still be a consequence of infection (e.g. impetigo), but can also be associated with inflammatory diseases (e.g. contact dermatitis, pemphigus foliaceous).

Vesicles are the result of fluid aggregation within the epidermis, or between the epidermis and dermis. Vesicles are uncommon, but may be associated with congenital diseases (e.g. epidermolysis bullosa simplex), sterile immune-mediated diseases (e.g. pemphigus vulgaris), viral infection (e.g. poxvirus), thermal injury, focal trauma, and severe contact allergy.

Technique: These lesions can be very fragile and it is important to get them off intact, so wider margins are ideal - be gentle and pick up by the panniculus! It is also critical that the pustule or vesicle is sectioned in by the lab so it can be seen by the pathologist - marginal skin sectioning may totally miss the critical primary lesion! There are a couple of options to avoiding this:

- elliptical incisions are ideal but slower and may risk rupture of delicate lesions
- use an 8mm punch, but request multiple deep recuts of the section to ensure the diagnostic lesion is present for viewing by the pathologist.

Note that if the punch is too small, it will cause the roof to come off the lesion, leaving a less or non-diagnostic ulcer or erosion.

Request Form Tips:

- *If a large punch is used it is important to write on request form 'Multiple deep recuts please' to ensure the pustule or vesicle is seen by the pathologist.*

Nodular & Draining Lesions

Basic Pathophysiology: Nodular lesions with overlying epidermis of normal thickness are a consequence of focal cellular accumulation in the dermis and/or panniculus. It may be infectious, sterile inflammatory, dysplastic (e.g. follicular cyst) or neoplastic. Severe inflammatory exudate may lead to focal necrosis or interfere with blood supply leading to a draining sinus.

Technique: Nodular or draining lesions will often have the diagnostic changes deep in the dermis and/or panniculus (e.g. sterile panniculitis, mycobacterial infections). As the causative lesion is deep in the skin, it is best to pick these samples up by the epidermis when handling to avoid crush artefact of the diagnostic parts of the specimen. As the epidermis is generally less important, in these cases it is often possible to surgically prep the surface without affecting the quality of the biopsy.

As mentioned previously, local anaesthetic can sometimes distort pannicular tissues, so where pannicular involvement is suspected, a ring block, regional anaesthesia or general anaesthesia is recommended.

Deep Tissue Cultures

Basic Pathophysiology: Deep tissue cultures are used where there is a suspicion of deep infection, often not responsive to standard therapies (e.g. deep bacteria pyoderma, mycobacterial infection). These are superior to skin swabs or wound stabs from draining tracts that simply may not get a significant sample from the deep infection, or often have significant surface contamination that may overgrow the primary infection, giving a misleading result.

Technique: The technique for deep tissue biopsies for culture is a little different to the standard skin biopsy technique:

- only intact affected skin should be biopsied; avoid sinuses and ulcers to minimise surface contamination
- the skin surface is aseptically prepared for surgery
- a sterile kit and new punch are used for the sample using aseptic surgical technique
- once the sample is taken, cut off the epidermis (about the top 25% of the biopsy) with a sterile blade to remove surface contamination, leaving dermis and panniculus only
- the sample is then placed in sterile saline-soaked swabs in a yellow top container then submitted for C&S as appropriate.

As previously mentioned lignocaine, bicarbonate and adrenalin can each inhibit various bacteria, mycobacteria and fungi. A ring block, regional anaesthesia or general anaesthesia is preferred in these cases.

Nodules / Tumours

Biopsies from tumours may be either incisional or excisional. Incisional biopsies should be considered

- if the lesion is too large to easily resect

- if biopsy is performed under local anaesthesia and sedation only
- if there is a difficulty of anatomical location e.g. limb, pinnae, nose, tail
- where follow-up surgery, if required for complete excision, can be done quickly

Punches from any central necrotic areas of a lesion should be avoided. If there are several lesions present a variety of lesions should be sampled, esp. if these lesions are not all similar because more than one disease process may be present, especially in older dogs.

Excisional biopsies are preferred where possible, and should be considered:

- if the lesion is easily excised under sedation and local anaesthesia
- if you have a strong suspicion of the diagnosis after fine needle aspirate of a benign tumour
- if the lesion is solitary or very few present
- as it gives better information esp. for small tumours
- if sufficient margins can be taken (but may need GA).

Assessment of tumor margins for completeness of excision is important for local control of neoplastic masses, and should be a consideration with excisional biopsies. Of the margin-marking techniques available, India inking seems to be the most practical way for veterinary clinicians to help pathologists accurately distinguish between surgical margins and margins created during sample processing. Simply using a cotton bud dipped in India ink and rolled over the cut surface of the biopsy should be adequate. India inking prevents misinterpretation of contaminated processing margins as inadequate surgical excisions; however, a strongly definitive decision that an excision is complete cannot be made with any margin-marking technique because it is impossible to examine the entire surface of every margin.

Request Form Tips:

- *For excisional biopsies that have been inked on the margins, write on the request form that 'margins have been inked' !*

WHO SHOULD THE BIOPSY BE SENT TO?

When considering where to send your biopsy samples, there are several criteria that should be fulfilled by a lab and pathologist.

- **A complete report**

  While most vets don't spend a lot of time reading the histopathological description, there are times when a scan of this part of the report may bring to light some problems with the conclusions (see notes on interpretation of the biopsy report below). A thorough comments section with notes on the firmness of the diagnosis (or possible differentials) is also very useful. Note that a good pathologist probably hasn't seen a live animal for many years, and should not make too many comments regarding treatment options - that is our job as clinicians!

  Take home message: Don't settle for a one line report.

- **Good communication**

  The ability to talk to the pathologist when things do not turn out as you expect or there are problems in the report may be critical to getting a diagnosis right.

- **A willingness to call a non-diagnostic sample non-diagnostic**

  While there is pressure on pathologists to make a diagnosis with every biopsy coming in, a good pathologist will resist this and call a non-diagnostic sample just that. Over-interpretation by a pathologist of vague or mixed histopathological changes can lead to misdiagnosis and inappropriate therapies.

- **Knowledge and experience**

  Where possible, the best lab pathologist to examine your skin section is a specialist pathologist with experience in dermatohistopathology, followed by a general specialist pathologist (or a resident with one of these as a supervisor). While there are several good non-specialist pathologists employed by companies in Australia, it is simply not possible for them to have the knowledge earned as part of the specialist training.

  Specialist dermatologists also are all trained in histopathology, and many routinely examine their own histopathology and give primary or secondary opinions on external biopsies. Their knowledge and experience with both the clinical and microscopic disease means that they can also be useful for information prior to biopsy for selection of appropriate lesions, and can offer clinically based advice on case management.

Note that specialist dermatologist histopathological experience is generally more with non-neoplastic skin diseases.

- **Turnaround time**

  While in most cases quicker is better, the pressure for a very rapid turnaround by pathologists can mean that on occasions some details may be missed. Be kind to your pathologist if this happens - they sometimes need to get through an astonishing number of biopsies per day. It is another good reason to read your biopsy report thoroughly to make sure things have not been missed!

- **Value for Money**

  The biggest expense for a client is where an incorrect diagnosis is pursued. The difference in cost between labs and pathologists is not great so it is important to find the one that works best for you considering the criteria above. Finding a lab that is happy to accept multiple specimens for skin cases at a reasonable cost is also a consideration. However, it is best not to shirk on cost if a few dollars can make a difference to getting the diagnosis right.

HOW DOES THE CLINICIAN INTERPRET THE HISTOPATHOLOGY REPORT?

While it is not the job of the clinician to interpret the histopathological findings, but it is the clinician's job to ensure that the findings of the biopsy report match up with the clinical findings on the patient. Each and every biopsy report needs to be critically evaluated and compared with the clinical details of the case before accepting the conclusions of the report because, unlike what many of us were taught at university, biopsy reports can be flat out wrong.

Why is this so? Pathologists can only report on what they see in that small piece of skin under the microscope, and they do not have the benefit of the entire patient in front of them when they make a diagnosis.

Several factors can contribute to the pathologist failing to make a diagnosis or come to the wrong conclusion:

- if the biopsy does not contain representative histopathological changes of the gross disease (through bad luck or bad lesion selection)

- if the biopsy has several pathological processes going on simultaneously
- if the biopsy is not from a disease with distinct histopathological changes (the skin can only react in a limited number of ways)
- if the diagnostic changes have been lost in sectioning.

As clinicians then, it is our job to make sure the report matches what we are seeing clinically, to make the ‘clinicohistopathological correlation’. Which brings us back around to asking ‘how does the clinician interpret the histopathology report?’

The Histological Description

The histological description is the pathologist telling you what they have seen. To many vets, this section of the report is seen just to contain a lot of jargon, and they skip through to the diagnosis and comments section. However, there are some key elements to look for here that can make or break a diagnosis.

If you submit a specific lesion for examination, you want to make sure that the pathologist has actually seen the lesion you want him or her to see and that it has not been lost in processing (e.g. pustules may be sectioned out, crusts may be lost in processing if not specifically requested to be examined.). The place to make sure the pathologist has seen what you wanted them to is in the histological description.

Sometimes more subtle lesions may be missed by the pathologist if you do not ask them to specifically look at them. Remember most pathologists are time poor also! Examples of this include alopecia areata (inflammation around the bulbs), dermatophytosis in some cats (fungal elements can be hard to find), or sebaceous adenitis (the skin can look histopathologically normal aside from the absence of sebaceous glands). Again, the place you need to check to see if the pathologist has specifically looked at these structures is in the histological description. The best way to ensure the pathologist looks specifically at the items you need them to is to send in a good history and differential diagnosis list! A pathologist would never not notice the sebaceous glands if you had sebaceous adenitis on your differential list!

Diagnosis

There are often two different diagnoses on the biopsy report - a morphological diagnosis and an aetiological diagnosis. Confusingly, these can appear under the same heading.

Aetiological Diagnosis

An aetiological diagnosis is the information everyone wants to see - the disease likely causing lesions seen clinically, i.e. pemphigus foliaceous, dermatophytosis, squamous cell carcinoma. For reasons already outlined, an aetiological diagnosis may or may not be present on the report.

It is important though that this information is not taken at face value or over-interpreted. The use of the words “probable” or “likely” prior to an aetiological diagnosis are a clue to go back and make sure that the changes seen histopathologically correlate with what you are seeing clinically before starting definitive therapy. If not, get a second opinion.

Even where the diagnosis seems clear cut from the pathologist’s point of view, it is important to remember that they don’t have the patient in front of them. If the diagnosis does not match what you are seeing clinically, talk to your pathologist first, and if things still do not make sense, then get a second opinion.

Morphological Diagnosis

A morphological diagnosis is a summary of the histopathological processes going on. While this gives the clinician an idea of what is going on in the skin it should absolutely not be taken as an aetiological diagnosis. An example of this is pyogranulomatous dermatitis, which may be caused by deep bacterial infections, deep fungal infections or demodicosis, or be a sterile immune mediated process. Vasculitis is another classic example that may be secondary to other diseases processes such as bacterial infections or allergies (esp. in cats), cutaneous histiocytosis, a drug reaction or may be a primary immune-mediated process.

The presence of a morphological diagnosis in the absence of an aetiological diagnosis means that further investigation will be required to sort out what disease is causing these lesions. Definitive treatment in most cases should not be started on the basis of a morphological diagnosis alone.

Comments

This is where the pathologist will try to put together the history you have provided with the histopathological changes they have seen to make sense of it all. Where uncertainties exist they are usually detailed here, even if they are not detailed in the Diagnosis section of the report. The key in reading the Comments section regarding the diagnosis is not to ‘read between the lines’ of what is written in this section but take it at face value.

For example, if the comment says ‘probable pemphigus foliaceous but the less likely chance of superficial bacterial pyoderma cannot be ruled out’, do not just reach for the prednisolone on the grounds that the pathologist is just being complete for completeness sake. The comment is likely there for a reason, and that is bacterial infection is still a possibility!

On the other hand, take treatment recommendations a little more lightly. Many pathologists would happily agree if asked that they have not treated an animal themselves for years, and as such treatment options for certain diseases may be available now that are unknown to the pathologist. Our job as clinicians is to know the most current and appropriate therapies for the treatment of disease. And as always, if unsure, then get a second opinion.

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Chapter 26

Recent Advances in Dermatological Diseases and Therapies in Dogs

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MALASSEZIA HYPERSENSITIVITY

Introduction

Malassezia pachydermatitis is a lipophilic, non-lipid dependent, nonmycelial saprophytic yeast with a thick walled oval or peanut shape. It is considered part of the normal flora of the ear canals, anus, lip, rectum vagina, interdigital areas and anal sacs in dogs. [1 2 3 4]

The conversion of *Malassezia* from a normal to pathogenic flora is a result of a combination of factors where there are alterations in the hosts immunological (development of hypersensitivity reactions) and non-immunological (failures of epidermal barrier function) defences. [1 5]

Pathogenesis and Immunology

Predisposing factors include: increased availability of nutrients (excessive sebum or cerumen); moisture accumulation or increased humidity seen in particular anatomic locations (intertrigo); long-term corticosteroid or antibiotic administration; hypersensitivity disorders (atopy, food allergy); parasitic infections; endocinopathies (hyperadrenocorticism, hypothyroidism); keratinization disorders - primary seborrhea, West Highland White Epidermal Dysplasia; metabolic or neoplastic disorders such as hepatocutaneous syndrome or paraneoplastic disease in cats with thymomas. [1 2 5]

Self trauma from pruritus causes further disruption to the epidermal barrier function.[2 6] When dogs become pruritic (such as occurs in the atopic dog) they may also be more exposed to *Malassezia* antigen than healthy animals. Licking can seed organisms from mucosal to cutaneous sites, where increased temperature, moisture, inflammation and trauma may facilitate antigen exposure to the immune system.

Malassezia adheres to the epidermis via expression of surface glycoproteins that enable it to bind to carbohydrate ligands expressed on the surface of canine corneocytes. [7] Once *Malassezia* has adhered to the epidermis, it can then penetrate the superficial layers of the stratum corneum. Ineffective barrier function in canine atopic skin facilitates this adhesion and absorption of antigen.[6]

Malassezia then triggers the immune system and the inflammatory cascade resulting in a Type-1 (immediate) hypersensitivity reaction to the soluble allergens produced by the yeast in the atopic dog. Normal dogs develop a Th-1 response and do not develop immediate hypersensitivity reactions. [2] [8]

The development of an immediate hypersensitivity reaction to *Malassezia* in the atopic dog is supported by positive intradermal skin test reactions, positive passive transfer by the Prasunitz-Kustner test [9] and the identification of increased IgE responses to *Malassezia* allergens by Western immunoblotting in atopic dogs compared to normal dogs.[10]

Malassezia allergens have been identified with molecular weights of 45, 52, 56 and 63 KDa (major allergens) in over 50% of atopic dogs with Malassezia but not in normal dogs. [10] Positive intradermal skin tests seen in dogs with atopic dermatitis with *Malassezia* infections had a greater wheal and flare than results in atopic dogs without *Malassezia* infections. Positive skin tests were not seen in normal dogs.[11]

In atopic human patients, specific *Malassezia* allergens that have been identified as rMala s1 and 5 – 9. rMala s 6 which appears to be a major allergen. [12] [13] [14] rMala s 6 (mw 17.2 kDa) is a protein with homology to cyclophilin, cyclophilin is considered to act as a “pan-allergen”. [12] [15] IgE sensitivity to *Malassezia* allergens is particularly found in atopic humans with dermatitis of the head and neck. [13] Nil to very low levels of reactivity to *Malassezia* allergens has been seen in healthy unaffected controls.[12]

Elevated IgG levels have been found in atopic dogs with or without Malassezia dermatitis. Normal dogs have significantly lower levels. [6] [16] A antigen of 25kDa in size was recognized in the atopic/malassezia dogs, but not in the other groups (atopic only, and normal). [16] The role of IgG remains unknown. Chen[16] hypothesized that IgG may be protective, increasing phagocytosis of the yeast by acting as an opsonin. Alternatively, it may activate complement and increase inflammation. Scott[2] considers that IgG and IgA do not appear to have any protective role as high levels are seen in the face of active ongoing infection.

In addition to expressing various allergens, *Malassezia* also produces inflammatory products that alter the sebum barrier of the skin, activate complement and amplify inflammatory reactions. These include various proteases, phospholipases, lipoxygenases, phosphatases and zymogen. [2 17]

Treatment

Treatment should be aimed at correcting primary diseases such as food allergy, atopy, parasitic or endocrine disorders, restoration of the epidermal barrier function, as well as formulating long term, practical measures. Treatment is unlikely to completely remove the infection as *Malassezia* is part of the normal flora.

Systemic therapy is usually required to control infection. An atopic dog with a *Malassezia* infection can experience a reduction in pruritus of 75 – 100% when the *Malassezia* infection is treated.[1] Suggested systemic therapies and doses are:

- ketoconazole at 5 – 10mg/kg once daily for 3 – 4 weeks and then pulsed at 5 – 10mg/kg two consecutive days a week.
- Itraconazole: 5mg/kg once daily for 3 – 4 weeks, or 5mg/kg two days a week for 3 weeks
- Fluconazole: 2.5- 5.0mg/kg once daily for 3 – 4 weeks
- Terbinafine at 30mg/kg once daily for 3 – 4 weeks.

Topical therapy is a useful adjunct, but in general, will not eliminate active infection. Topical therapy is of more value in maintenance and prevention of relapse.

Immunotherapy

A commercial extract of *Malassezia pachydermatis* is produced by Greer Laboratories and is available for use in Australia for intradermal skin testing and subsequent desensitization. The threshold concentration for skin testing is 1,000 pnu/ml (protein nitrogen units). This concentration of allergen is the highest concentration that does not produce positive results in greater than 90% of normal individuals.[8] In Farver's study[8], 93% of atopic dogs with malassezia dermatitis, had positive intradermal skin test reactions to Malassezia extract. 100% of atopic dogs with Malassezia otitis only, tested positive, but numbers of dogs were low. 31% of atopic dogs without Malassezia infections, tested positive. No normal dogs in this study tested positive at the 1,000pnu dilution. At present, no serum IgE tests can be recommended.

In a recent multicentre study, atopic dogs on immunotherapy, with persistent *Malassezia* dermatitis and pruritus that still required anti-fungal therapy, were given 1,000pnu *Malassezia pachydermatitis* allergens, once weekly. Response was excellent in 2 of 4 dogs and the remaining two had a significant reduction in pruritus once *Malassezia* was added to the desensitization schedule. [1]

ALOPECIA X

Introduction

Alopecia X has also been called adrenal hyperplasia-like syndrome; adrenal sex hormone alopecia; congenital adrenal hyperplasia-like syndrome; (adult onset) growth hormone responsive alopecia; castration responsive alopecia; adult-onset hyposomatotropism; gonadal sex hormone alopecia; follicular dysplasia of Nordic breeds; pseudo-Cushing's; Lysodren responsive dermatosis; and biopsy-responsive alopecia.

Alopecia may be classified as being traumatic (eg self-inflicted) or non-traumatic. Non-traumatic alopecia can be subdivided into inflammatory hair loss, as seen in bacterial folliculitis or demodicosis, or non-inflammatory. Non-inflammatory alopecia is further subdivided as hair loss due to either abnormal hair growth (as in colour dilution alopecia) or abnormal hair cycles.[1]

There are three phases in the cycle of hair growth. Anagen is the active growth phase of the hair follicle. Anagen hairs have a distinct hair bulb and dermal papilla and fully formed inner root sheath. Telogen hairs have completed growth. The dermal papilla is small and the inner sheath is replaced by tricholemmal cornification. As a hair cycles from the active anagen to the quiescent telogen stage, it passes through catagen. This can be considered an involutionary stage of the hair follicle. [1] [2]

Alopecia X is a non-inflammatory, non-traumatic alopecia and at present, the pathomechanisms remains unknown but are considered multifactorial. There is evidence it is due to a defect of the receptors at the follicular level or as yet an unidentified hormonal imbalance. This results in hair cycle "arrest" with hairs held in prolonged telogen and failing to enter the anagen phase. [1 3 4]

Cerundolo et al [5] has hypothesized that *Alopecia X* is a mild form, or variation of, pituitary-dependent hyperadrenocorticism in certain breeds such as the Pomeranian. Cerundolo [5] has documented increased serum 17-hydroxyprogesterone (17-OHP) and mild increases in cortisone production and excretion, in affected dogs. Progesterone can be also be elevated in these dogs. Progesterone has an anti-androgenic action. Increased progesterone, leads to low levels of androgens and this local effect causes hair loss. Some dogs respond to testosterone supplementation but others do not. Growth hormone may change the sensitivity of the hair follicles to sex hormones, or a growth hormone deficiency could be induced by other intercurrent endocrinopathy.

Clinical Signs

The syndrome is quite common and is seen in plush coated dogs such as Pomeranians, Chow Chows, Keeshonds, Samoyeds, miniature Poodles and Nordic breeds.[1 3] It is interesting to note that affected dogs are often described by their owners are having particularly dense coats as puppies. There is a progressive and gradual loss of guard hairs that begins on the frictional zones of the neck and spreads to include the tail, caudal thighs and trunk. The head and limbs are usually spared. [1 2 6] The alopecia is bilaterally symmetrical and the exposed skin becomes heavily hyperpigmented. Tufts of hair may regrow at sites of trauma such as biopsy. Animals do not show others signs of systemic illness or endocrine imbalance and are not pruritic. [1 4 5]

The hair loss usually begins at 1 - 2 years of age, but has been reported in dogs up to 10 years of age. Some authors report that males (intact or castrated) are more affected than females, while Frank[1] has observed it equally in males and females, whether intact or neutered.

Diagnosis

Differential diagnosis for non-inflammatory, non-traumatic alopecia include: numerous endocrine dermatosis: hypothyroidism, hyperadrenocorticism, hyposomatotropism, gonadal sex hormone imbalance, and adrenal sex hormone imbalance, *Alopecia X*; and non-endocrine dermatosis: *Alopecia X,* post-clipping alopecia, cyclic (or recurrent) flank alopecia and anagen/telogen defluxion.

Diagnosis is made by collecting a thorough history, physical and dermatological examination (skin scrapes, trichograms, fungal cultures), and histology (to rule out other causes of hair loss such as dermatophytosis, sebaceous adenitis and follicular dysplasia). Histology does not help differentiate between *Alopecia X* and other endocrinopathies as they all share many histological changes such as follicular and sebaceous gland atrophy and telogenization, hyperkeratosis, tricholemmal keratinization (flame follicles) etc.

It is essential to rule out other endocrine disorders, in particular, hypothyroidism and hyperadrenocorticism. Animals should be assessed for evidence of sex hormone dermatosis, especially if intact, such testicular tumours in males and failure to cycle in females.

Interpretation of adrenal sex hormones can be difficult, as evidenced by a study in 1990 by Schmeitzel [7]. She studied normal and affected Pomeranians and measured their adrenal sex hormone levels pre and post ACTH stimulation. She found increased progesterone, dehydroepiandrosterone sulfate and androstenedione levels after ACTH stimulation suggesting a deficiency of 21-hydroxylase, an enzyme involved in adrenal sex-hormone metabolism. However, these changes were found in both groups of dogs, normal and affected. [2] [7]

This difficulty in interpretation and use of adrenal sex hormones for diagnosis in cases of endocrine alopecia has also been found in a large retrospective study of 276 dogs with endocrine alopecia. [6] In this study, 73% of dogs had at least one basal or post-ACTH steroid hormone above the normal range and the most common of these hormones was progesterone. They were not able to establish reference ranges for hormone concentrations (oetradiol, progesterone; 17-OH progesterone and DHEAS) for normal dogs of specific breeds, suggesting different values for different breeds. They concluded that if the alopecia was not a result of hypothyroidism or hyperadrenocorticism, it was difficult to establish a consistent steroid hormone imbalance in the other cases.[6]

Treatment

Clinicians should remember that in many cases this condition is a cosmetic disorder and that treatment options have the potential for significant side effects and associated economic costs.

Treatment options may use various stimuli (including different hormones) that stimulate hair follicle receptors and trigger the hair to enter the anagen phase of the hair cycle, or medication to correct abnormal adrenal hormone synthesis. [3] [4]

Melatonin is a neurohormone produced by the pineal gland in response to decreasing day length. It is a product of the conversion of L-tryptophan to serotonin and then to melatonin. It is involved in the control of reproduction, thermoregulation, seasonal coat growth and colouration, and photoreception. In humans it has been used for a variety of conditions such as sleeping disorders, jet lag, depression and contraception. [9]

Melatonin results in hair regrowth in approximately 40 – 60% of dogs. The dose is 3 – 5mg per dog, two to three times daily. [3] [4]

Some studies have found a correlation between changes in sex hormones and positive response to melatonin therapy, and others have not. In one study, intact dogs were given 28 days of melatonin therapy. In intact females, there was decreased oestradiol, testosterone and dehydroepiandrosterone sulfate (DHEAS). In intact males, a decrease in oestradiol and 17-hydroxyprogesterone (OHP) was seen. This suggests that melatonin suppresses gonadal sex hormones and that this suppression allows hair follicles to escape telogen and enter anagen [9].

In another study [3] no significance difference was seen in sex hormone levels after four months of melatonin therapy. However, the dogs in this study were neutered and their sex hormone production was from the adrenals only. In these dogs, partial to complete hair regrowth was seen in 62% of cases. There was no correlation between response to treatment and changes in cortisol or adrenal sex hormone concentrations. This suggests that melatonin may act at the level of the hair follicle receptor directly, or by hormones we remain unable to identify and measure.

Melatonin failure may be due to incorrect dose, poor absorption; incorrect timing of medication (daylight, evenings, season), or quality of the drug as melatonin production is not standardized nor quality controlled. [3]

Trilostane is a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, an adrenal enzyme that converts pregnenolone to 17-hydroxypregnenolone and cortisol. In Cerundolo's study [5] of 24 dogs with signs of *Alopecia X*, increased urinary cortisol/creatinine ratios and elevated 17-hydroxyprogesterone, and were treated with a mean dose of trilostane at 10.85mg/kg daily. Complete hair regrowth was achieved in 85% of Pomeranians and 100% of Poodles within 4 – 8 weeks. In many of these dogs, trilostane was able to be successfully reduced to three times weekly without relapse of hair loss. The effectiveness of trilostane may have been due to down regulation of adrenal steroid synthesis or noncompetitive inhibition of the oestrogen receptors at the hair follicle level. If benign neglect for this cosmetic disorder is not acceptable to owners, then trilostane may be recommended. [5]

Mitotane has a cytotoxic effect on the adrenal cortex (zona fasciculata and reticularis) and interferes with steroid biosynthesis by inhibition of the 11β-hydroxylase enzyme in the cortisol production pathway. It has been used with varying results in cases of *Alopecia X*. Hair regrowth ranges from partial to complete. Mitotane has been potential serious side effects such as Addisonian crisis that must be considered before recommending its use. [3]

Neutering produces variable results. Hair regrowth may occur in males once castrated, but this regrowth may be temporary only. [5]

Growth hormone has been successfully used in some cases as a trigger to the follicle receptors and also when a GH deficiency has been diagnosed by a xylazine response test. However, growth hormone is diabetogenic and is now difficult to obtain.

To conclude, the cause of *Alopecia X* remains unclear. However, there is evidence that it involves hair follicle receptor defects and also hormonal imbalances. Once endocrinopathies such as hypothyroidism and hyperadrenocorticism are ruled out, further diagnostic tests for adrenal sex hormone disorders are difficult to interpret. Clinicians must remain vigilant to monitor for signs of gonadal sex hormone disorders such as hormone secreting tumours. If absent, then the condition may be considered a cosmetic disorder and no therapy is required. However, the use of melatonin is often successful in triggering hair regrowth without creating adverse side effects. Trilostane also appears to be very successful in the treatment of *Alopecia X*, but there are associated risks of adrenal necrosis and considerable cost to the client.

ACRAL LICK DERMATITIS

Introduction

Acral lick dermatitis (ALD) is also called acral lick granuloma or acral pruritic nodules. ALD is a relatively common and self perpetuating disorder associated with chronic licking. It is a chronic and frustrating disorder to treat, with response to therapy prolonged, and relapse not uncommon. In addition, there are numerous primary and perpetuating factors involved in the pathogenesis of this disease. These must be identified, corrected or avoided if possible.

Canine acral lick dermatitis is analogous to *Lichen simplex chronicus* in man. This is described as a localized circumscribed thick area of skin with lichenification due to repeated rubbing and scratching. In dogs, the excessive licking causes production and release of endorphins. Endorphins produce an analgesic and europhoric effect, decreasing the animal's perception of pain and perpetuating the itch/scratch cycle. In man, the lichenified skin becomes an erogenous zone and becomes a pleasure to scratch. Rubbing and itching becomes habitual and unconscious.

Signalment and Clinical Signs

Constant licking creates a firm, oval plaque or nodule with an eroded or ulcerated surface covered by a tenacious purulent exudate. There is a hyperpigmented halo around the periphery and the surrounding hair is salivary stained. Acral lick dermatitis affect the cranial aspect of lower limbs and may be solitary, or affect multiple limbs.

ALD is commonly seen in large breed, active, affectionate dogs – the Golden and Labrador retrievers, Great Danes, Irish Setters, Boxers, Dobermans, German Shepherds and St. Bernards. However, they can also develop in smaller breeds. Dogs are usually older than 5 years of age when lesions develop. Males are affected greater than females at a ratio of 2:1. Certain breeds, such as the Doberman or Great Dane tend to develop ALD due to psychogenic disorders, while breeds such as the Retrievers, often have an allergic disorder complicated by the presence of secondary pyoderma.

Pathogenesis

Primary factors that trigger the constant licking include: hypersensitivity diseases (fleas, atopy, food allergy, contact allergy), infectious diseases (bacterial, fungal, demodicosis, scabies); wounds or foreign bodies; trauma; neoplasia (histiocytomas, SCC, mast cell tumours); musculoskeletal or neurogenic diseases; and psychogenic disorders. Perpetuating factors include: deep pyoderma; osteomyelitis; release of ruptured hair shafts and keratin in the dermis (acting as foreign bodies); arthritis and the development of learned behaviour.

Psychogenic disorders may be triggered by an environmental change, such as the loss of a companion dog, changes to clients work hours, or prolonged boarding which results in restricted activity or stimulation. The combination of boredom and additional stresses such as separation anxiety, can then lead to the development of canine compulsive disorder (analogous to human obsessive-compulsive disorder).

There are similarities between human obsessive-compulsive disorder and ALD in the dog. Serotonin is a neuromodulator. It facilitates tonic motor actions and inhibits sensory perception. In man with OCD, serotonin levels are low. It is proposed that the repetitive motions (hair pulling etc) of OCD increases serotonin neuronal activity.

Diagnosis

Due to the multifactorial and chronic nature of the disease, diagnosis should not be made by clinical appearance alone.

Diagnostic tests include: cytology by impression smears or fine needle aspiration; bacterial tissue cultures; fungal cultures; skin scrapes; radiography; allergy testing (food trials, intradermal or serum allergy testing); and histopathology.

It is essential to also obtain a detailed history, with focus on triggers such as boarding, illness or injury, or additional evidence such as seasonality, that supports underlying hypersensitivities. Should the history, clinical examination and any of the laboratory tests fail to identify any primary factors, then assessment for behavioural disorders is essential.

Histopathology

ALD's are not a true granuloma. It is epithelial hyperplasia and fibrosis that produces the characteristic plaque. Histologically, there is irregular marked epidermal hyperplasia and hyperkeratosis, erosion or ulceration which may be focal or extensive, perivascular neutrophils and mononuclear cells (mild), vertical streaked fibrosis (fibroblasts and collagen fibrils), moderate to marked plasma cells around adnexa, especially distended apocrine sweat glands and inferior segments of hair follicles, and sebaceous gland hyperplasia. Folliculitis and furunculosis may also be seen.

Treatment

The prognosis for acral lick granulomas has been considered by many to be guarded. The key to success is to treat early and aggressively, to identify and correct primary and perpetuating factors: for example, diagnose and manage underlying hypersensitivities; identify and appropriately treat infections that develop secondary to the constant licking and trauma; and to remove stress in the dog's lifestyle. The itch/scratch cycle can be broken with the use of Elizabethan collars and dressings, but many dogs begin to lick other sites if access to primary site is restricted without addressing the primary disease.

Infection

ALD'S are areas of deep bacterial folliculitis and furunculosis and require long term antibiotics. Antibiotics are used for at least 2 – 4 weeks past clinical resolution and a 6 – 8 week (or longer) course of 20 – 30mg/kg cephalosporins should be expected. Fluoroquinolones have particular use if gram negative organisms are identified, or if fibrosis and scarring is present. If lesions do not respond, then deep tissue culture and sensitivity should be performed and biopsy recommended. Where complete resolution is never achieved, pulse antibiotic therapy can be used.

Hypersensitivity

The treatment of choice for atopic dermatitis is allergen-specific immunotherapy (desensitization) that is based on results of intradermal skin tests or serum Ig E tests. Food allergy is diagnosed by following a strict food elimination dietary trial for 6 – 10 weeks followed by a dietary challenge. Individual allergens (proteins) can be identified and then avoided. The FAD dog must be protected from fleas with quality products, administered all year round, at appropriate doses.

Topical or systemic corticosteroids should be avoided until all evidence of infection has been resolved and after dogs have been investigated for hypersensitivity disorders. Cyclosporine can also be used to control ALD where the primary factor creating pruritus is underlying hypersensitivities.

Psychogenic

Treatment of psychogenic disorders requires a holistic approach. Environmental enrichment, medication, changes in socialisation, activity and training is required for successful management. A lag phase of four to five weeks after beginning medication should be expected. Therapies include: selective serotonin reuptake inhibitors eg citalopram, fluoxetine (Prozac®); tricyclic anti-depressants. eg. clomipramine (Clomicalm®), amitriptyline (Endep®); anxiolytic drugs e.g. doxepin, hydroxyzine; narcotic antagonists (endorphin blockers) are expensive and lesions tend to relapse once medication is discontinued. e.g. naltrexone, nalmefene; endorphin substitution supplies an exogenous endorphin thus eliminating the urge to lick, and allowing the lesion to heal. e.g. hydrocodone 0.25mg/kg q8h.

Additional Therapies

Topical Therapy

DMSO is an organic solvent and acts as a vehicle that carries active ingredients such as glucocorticoids through the epidermis. DMSO also has anti-inflammatory properties. It is formulated as DMSO-fluocinolone acetonide as a twice daily product. It can also be combined with flunixin, a prostaglandin synthetase inhibitor.

Capsaicin (HEET) is an analgesic, and can be mixed with bitter apple (1:2 ratio) BID to TID help early lesions. Capsaicin causes substance P release from nerve ending. Substance P is a neurotransmitter involved in communication of pain and itch from cutaneous nerve endings to the central nervous system**.** Substance P release results in mast cell degranulation and inflammation. Prolonged and repeated use of capsaicin depletes the store of substance P from nerve endings, thus reducing pruritus.

Mupirocin (Bactroban®) twice daily to the lesion. Mupirocin penetrates fibrotic tissue very well. It is an effective antibiotic cream and does not contain glucocorticoids.

Intralesional glucocorticoids is reported to help in early or small lesions, but ineffective in chronic large lesions. It should be used cautiously due to presence of secondary infection.

Acupuncture

Acupuncture is reported to be effective in the treatment of acral lick granulomas. It is believed that it increases local circulation, promotes healing, produces local analgesia, and relaxes the hyperactive animal, thus suppressing endorphin release. Traditionally, acupuncture restores the flow of ”Qi”, a chinese term for energy or life force. Qi exists just below the skin along pathways called meridians. Above the meridians, along the skin, are areas of increased peripheral conductance and decreased electrical resistance. These punctate areas are known as acupoints. Acupuncture needles are placed over these acupoints. By stimulating the acupoints over a meridian, the flow of Qi is regulated and restored. Acupuncture is used once to twice weekly. Half-inch needles are placed at approximately 5mm intervals at the junction of normal/abnormal tissue around the acral lick granuloma. They are directed towards the centre of the lesion. This technique of needle placement is termed “circling or surrounding the dragon”. Other needles are sited along the acupuncture meridian points traversing the lesions on the affected limb.

Electroshock Training Collars

One study reports the use of these collars in one hour training sessions once daily. 13.2 ms of shock resolved ALG in four dogs (note that 10 dogs were initially in the study, six dropped out due to client non-compliance and two of the four relapsed within six to twelve months). Resolution was defined in a one month follow up period and the relapses that occurred resolved with a repeated training period. The ethics in the use of such treatments in animals should be considered.

Laser Therapy

Vaporizes tissue and removes lesions with little pain and is reported to be quite successful.

Radiation Therapy

Resolved 35% of cases with no recurrence, 24% resolved but did recur within a year. Radiation is considered most effective when lesions are small.

Cobra Venom

3.3 to 50 mouse units injected in a horse shoe pattern proximal to the lesions. Injections may be given up to 3 times. Not available in Australia.

What Doesn't Work

- Mechanical protection of lesions (collars, dressing) used as a sole therapy
- Repellent liquids and creams
- Surgical resection may be considered in cases of severe fibrosis affecting limb mobility, these would often require skin grafts. The risks of wound dehiscence and the creation of larger more complex lesions is high and should be considered before acral lick granulomas are surgical removed.

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SPINOSAD

Flea allergy dermatitis (FAD) remains the most common hypersensitivity disorder seen in veterinary clinical practice despite the wide availability of relatively effective topical products for well over a decade. Client compliance remains the major cause of flea control failure. Clients fail to follow instructions, often only apply products once fleas are seen, do not treat all household pets, do not treat the environment and often do not protect their pets over winter. Clients are reluctant to use topical products due to their concerns over toxicity. This fear is exacerbated by localized cutaneous reactions that some animals display, such as erythema or pruritus, to the vehicles contained in these "spot-on" products. There are justifiable concerns over the potential of toxicity to cats when permethrins are applied to companion dogs. Resistance to the topical insecticides is also suspected as a cause of flea control failure.

Flea control products should have a rapid, yet prolonged adulticidal action and also possess insect growth regulator activity thus targeting the life cycle of the flea at various stages. This offers clients and their pets "integrated flea control". Products should have a wide safety margin, be easily administered to and well tolerated by pets, have a prolonged period of action, and not create resistance in the flea population.

In Australia, available topical products include: imidacloprid (Advantage®, Bayer), fipronil (Frontline®, Merial), selamectin (Revolution®, Pfizer Animal Health, and permethrins/parenthood products (eg. Permethrin®, Dermcare). Systemic products available include: lufenuron (Program®, Novartis) and nitenpyram (Capstar®, Novartis).

Spinosad (Comfortis®, Elanco) is an oral insecticide available for flea protection and prevention in dogs in Australia. It is not registered for use in cats. It has been available in the U.S.A for two years. It has previously been used in the agricultural field to protect crops from a variety of pests.[1] It offers an alternate to topical flea products. It is an adulticide and has no ovicidal activity.

Spinosyns are produced by fermentation of the naturally occurring soil bacterium actinomycete, *Saccharopolyspora spinosa.* Spinosad contains spinosyn A (major active component) and spinosyn D (minor active component). It is a novel, nonantibacterial, macrolide with a tetracyclic ring system with amino and neutral sugars attached. [1 2 3 4]

The spinosyns have several modes of action that target the insect but not the mammalian nervous system. [2 3] They bind irreversibly to as yet unidentified nicotinic acetylcholine receptors (nAChRs), thus disrupting acetylcholine neurotransmission. They also affect γ-aminobutyric acid (GABA) neurotransmission in the flea. Spinosyns are chemically unrelated to other flea products and do not interact with the known nicotinic or GABA sites the other flea control products target. This is of importance when dealing with resistance to products such as imidaloprid or avermectin. [1]

The consequence of binding to these receptors is to disrupt the insect's nervous system and create a state of hyperexcitation, involuntary muscle contractions, and tremors. The prolonged hyper-excitation of the motor neurons results in fatigue, paralysis and rapid death of target insects. [3]

Spinosad is presented as a beef flavoured tablet. The beef flavour is artificial and created using hydrolyzed soy and pork. Palatability is reported to be good with 77% of dogs eating the tablets by free choice. [3] It is best given with food to increase absorption and bioavailability and absorption is almost complete within one hour of ingestion.

The most effective dose rate to achieve a 97.2 -100% kill over a 30 day period is 30 – 40mg/kg once monthly. Therefore the recommended dose rate is a minimum of 30mg/kg every 30 days. Lower dose rates of 15 – 20mg/kg achieve excellent control over a two to three week period, with a decline in efficacy after that time. It is registered for use in dogs and puppies over 14 weeks. [2] [4]

Side effects are most commonly reported after the first administration of the drug. Their incidence appears to decrease over successive treatments. The most commonly reported side effect is vomiting. In one study, vomiting was reported in 12.7% of cases in the first month, reducing to only 5.8% by the third month. [3] Other reported adverse reactions were inappetance (8.8% reducing to 1.9% by the third month), lethargy (7.6% reducing to 1.2% by the third month), diarrhoea (6.7 % reducing to 1.2% by the third month) and cough. [3]

Spinosad has a very rapid rate of kill of adult fleas and this is seen within 30 minutes of drug administration. At four hours post administration, there is a kill efficacy of over 81% and by 24 hours the rate of kill is 100%. This 100% kill rate at 24 hours is maintained for three weeks after drug administration, and then reduces to 90% by 30 days. This rapid adulticidal action also has a significant affect at reducing egg production and environmental recontamination, and also reduces signs of FAD. [2] [3] [5]

Spinosad also has a rapid and prolonged affect on the flea count. [3] In a study of 470 dogs, flea counts on flea infested dogs reduced by 98.6% at 15 days post therapy. After three monthly treatments of spinosad, flea counts reduced up to 99.9% in these animals. As flea counts on these FAD dogs declined there was also a concurrent significant improvement in clinical signs of FAD: erythema (reduced by 100%), papules (100%), scaling (89%), pruritus (96%), and alopecia (100%). [3]

Its use in breeding or nursing bitches is not recommended. [6] In a study of 30 pregnant bitches [6], there was no significant difference in the number or their viability of the pups produced between bitches in a placebo group and a group of medicated bitches. There were three reports of pregnancy failure. One bitch had a late term abortion. Two bitches experienced early pregnancy failure, but these two dogs had had abnormal oestrus cycles prior to drug administration. The researchers were unable to establish a direct correlation between the product and pregnancy failures as a certain percentage of natural pregnancies fail. [6]

The combination of spinosad and ivermectin should be used cautiously. It has been reported that adverse reactions have been seen in non-collie breeds of dogs on extra-label, high dose ivermectin used for the treatment of demodicosis or sarcoptic mange.[4] These reactions were consistent with those seen in ivermectin toxicity. They included trembling, excess salivation, seizure, ataxia, mydriasis, blindness and disorientation. It is believed that this potentiation of ivermectin toxicity is a result of competition for the p-glycoprotein pump across the blood-brain barrier. Spinosad is a p-glycoprotein substrate and has a higher affinity for the pump than ivermectin. Spinosad and ivermectin enter the brain and drug concentrations begin to accumulate. Spinosad is preferentially pumped back across the blood brain barrier, resulting in a build up of ivermectin and the development of toxicity. It is recommended that spinosad should not be given for 15 – 30 days after the last high dose ivermectin has been given.[4]

In the future, Spinosad may have use in the treatment and protection against tick infestations. There has been a preliminary study on the use of spinosad against the brown dog tick, *Rhipicephalus sanguineus*. [6] In this randomized block, blinded study, 12 dogs were infected each week with 50 unfed ticks. The dogs were then given either a negative placebo control, or spinosad at 50mg/kg, or spinosad at 100mg/kg per os. At 24 hours, there was a significant decrease in tick counts of 94.8 and 97.2% in the 50mg/kg and 100mg/kg treatment groups respectively. However, by one month, this reduction had dropped to only 5% in dogs in the 50mg/kg group and 71.3% in dogs in the 100mg/kg group. It appears from this study, that spinosad has some efficacy against ticks. Further work to examine its efficacy against other tick species is required. [6]

Spinosad appears to be an effective long-acting adulticide against the flea. It has a rapid rate of flea kill and also has extended effects on reducing flea count numbers on dogs. It efficacy is not affected by repeated washing or swimming. The side effects of vomiting are not uncommon, but animals do appear to tolerate the drug better on repeated doses. It should not be given with extra-label doses of the avermectins, nor in pregnant bitches. It does appear to significantly alleviate clinical signs of flea allergy dermatitis in the dog.

TRILOSTANE

Trilostane is a relatively new therapy for canine and feline Hyperadrenocorticism (HAC) and Alopecia X.[1] HAC may be pituitary dependent (PDH) in 80 -85% of cases or due to cortisol secreting adrenal tumours (AT) in 15 – 20 % of cases. [2] The overwhelming majority of PDH arises from are benign tumours, while 50% of adrenal tumours are malignant.[2] The clinical signs of HAC are consistent with prolonged elevated circulating cortisol levels on multiple organ and metabolic systems. Treatment aims at reducing cortisol levels and may be achieved by either medical or surgical means. At this point in time, there is no medical cure of PDH available.

Trilostane is an oral, short-acting, synthetic steroid analogue that inhibits the adrenal enzyme, 3β- hydroxysteroid dehydrogenase in the adrenal gland. Inhibition of the enzyme suppresses conversion of pregnenolone to progesterone, and its subsequent conversion to cortisol and to a lesser extent, mineralocorticoids and sex hormones. It is also believed to influence additional enzymes such as 11 β-hydroxylase and11β-hydroxysteroid dehydrogenase, to further reduce cortisone and aldosterone levels. [3] [4] Enzyme inhibition is considered reversible and short acting over 20 hours to several days, but in some cases, animals experience enzyme suppression lasting weeks to months. [5]

Trilostane is effective in reducing cortisone levels, in most, but not all dogs with PDH and survival rates compares very well with mitotane.[6] In AT, trilostane will suppress cortisone secretion but not tumour growth. It has been used successfully to treat HAC in horses [7] but only creates a partial response in humans. [8] Trilostane is of considerable value for patients with PDH, in patients with concurrent disease such as diabetes mellitus, in patients with AT who are not surgical candidates, or to prepare patients with AT for surgery by improving general body condition. [5] Trilostane is expensive.

Adverse reactions are considered mild by some clinicians[3], but others have had experienced patient deaths with its use. [9] Side effects experienced are usually short lived due to the transient effect of the drug and include: lethargy, vomiting, (up to 63% of cases), diarrhoea, inappetance, weakness, lameness, severe depression, collapse, adrenal necrosis, Addisonian crisis and death. [3] [9] [10]

Contraindications for use include animals with primary hepatic disease or renal insufficiency; pregnant animals; animals on angiotensin-converting enzyme (ACE) inhibitors; or potassium sparing diuretics such as spironolactones. [10] It is metabolized in the liver and excreted in bile and urine.

If converting from mitotane to trilostane, give a month washout period to avoid an Addisonian crisis due to mitotanes prolonged affect on adrenal function. If treating *Malassezia* dermatitis with systemic ketoconazole, dose rates need to be adjusted to avoid an Addisonian crisis as ketoconazole also affects steroid synthesis.

Dose Protocol

There are no consistent recommendations and protocols available regarding induction and maintenance dose rates or frequency, timing of post pill sampling, or selection of tests used to evaluate response. [3 5 9 10 11] Clinicians should expect to adjust doses for at least 50% of individual dogs during therapy. [3 5].

Trilostane is available in 30mg, 60mg and 120mg size capsule and absorption is increased when given with food.

Dose Rate

To summarize, dose rates vary between 1-2mg/kg to 16.7mg/kg daily.

Recommendations include:

- Braddock [5] gave a mean daily dose of 16.7mg/kg, starting at 10mg/kg daily and adjusting as required to successfully treat 29 of 30 dogs Larger dogs appear to require lower doses per kg than smaller dogs. [5 9]
- Behrund [3] recommended a daily dose of 2-10mg/kg.
- Neiger [12] also gave dogs < 5kg - 30mg SID ; dogs 5 – 19.9kg - 60mg SID and dogs > 20kg - 120mg. The mean starting dose was 5.9mg, and was adjusted according to response to therapy.
- Ruckstuhl[7] used a mean daily dose of 6.1mg/kg.

Dose Frequency

It is usually administered once daily and achieves satisfactory clinical control and client compliance. However, twice daily dosing results in superior control, prolonged survival times, and a lower daily dosage required to control the disease. [9]

Dose Rate Adjustment

Dose rates for individual dogs are adjusted according to resolution or relapse of clinical signs, combined with results of ACTH stimulation tests and/or urine creatinine/cortisol ratios (UCCR). [3]

As trilostane is short acting, ACTH stimulation tests are best performed 4 – 6 hours after drug administration. [3] UCCR are best performed on samples collected prior to the drug administration (morning). [5 9]

Polydypsia and polyuria are reported to resolve within seven days [12] to 10 - 28 days [11] after beginning therapy in a total 70% of dogs.[11] Lethargy resolves in three weeks; panting within four and a half weeks; polyphagia within six weeks; potbellied appearance within ten and a half weeks; and skin conditions, a median of seven weeks [12] to three months [11] in the majority (62%) of dogs. This is consistent with the resolution of signs seen with the use of mitotane. [2]

An ACTH stimulation test is used to assess remaining adrenal function after therapy and adjust the dose as required.

ACTH stimulation tests should be performed 4 – 6 hours after medication, on day 10 to 14, 30 and 90 days on full dosing of trilostane.[3] If levels are between 20 – 200 nmol/L and clinical signs controlled, medication continues unchanged. If post-stimulation levels fall below 20nmol/L, then trilostane should be discontinued for several days and then started at a lower or alternate day dose. If clinical signs persist or levels rise above 200nmol/L, then the dose should be increased, or given twice daily. Long term monitoring of ACTH stim tests should be done every 3 – 6 months. [11]

However, trilostane has only a few hours of activity. ACTH stimulation tests at 4 – 6 hours post therapy may not fully evaluate the extent of enzyme inhibition over a 24 hour period. Dogs with a normal ACTH stim test may have periods of time when cortisol levels escape satisfactory control.

UCCR at the end of the 12 or 24 hour dosing periods may be a more accurate indicator of therapeutic efficacy. [12] UCCR $< 15 \times 10^{-6}$ was considered as showing good control of HAC. [5]

To summarize, the selection of dose rates and frequency of trilostane to treat HAC, should combine results of an ACTH stimulation test 4 – 6 hours after dosage, results of a UCCR prior to dosage and importantly, resolution of clinical signs. Trilostane does have the potential to create adrenal necrosis and careful monitoring is still required.

Mitotane is a chlorinated hydrocarbon (o,p'-DDD), related to the insecticide DDT [2 10]. It creates selective necrosis of the zona fasciculata and zona reticularis of the cortex of the adrenal glands. Mitotane is considered an effective treatment for PDH, and in AT where surgery is not considered a therapeutic option. Mitotane has a relatively high frequency of relapses, can be poorly tolerated by patients, and has a higher risk of hypoadrenocorticism with prolonged use. [2] [11]

Ketoconazole is a triazole antifungal drug which inhibits cytochrome P450 enzymes involved in the synthesis of adrenal steroids. It may also antagonize peripheral glucocorticoid receptors. [3] It is considered less effective in its treatment of HAC than other medical options. Suggested dose rates vary from 5mg/kg BID to 20mg/kg BID. [2] Most dogs appear to be well control at 10mg/kg BID. [2] Side effects at this dose are not uncommon and include: anorexia, vomiting, diarrhea and hepatotoxicity.

Selegiline (L-deprenyl), is an irreversible inhibitor of monoamine oxidase B, and therefore inhibits degradation of dopamine. Elevated dopamine levels suppress ACTH secretion from the intermediate lobe of the pituitary. Its efficacy is limited to some cases of PDH where the tumour arises from the intermediate lobe (only 20% of cases) but does not treat cortisol secreting adrenal tumours where ACTH levels are already suppressed.[2],[11]

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Chapter 27

Recent Advances in Dermatological Diseases and Therapies in Cats

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DERMATOLOGICAL DISEASES

Feline Herpesvirus Ulcerative Dermatitis

Feline herpesvirus ulcerative dermatosis is an uncommon, predominantly feline facial skin disease caused by herpesvirus infection. Testing by polymerase chain reaction (PCR) and DNA sequencing recently showed that the virus recovered from cats with this facial skin disease was indistinguishable from feline herpes virus 1 (Hargis et al 1999). FHV-1 is the major cause of upper respiratory and ocular disease in cats. Infection of susceptible kittens with FHV-1 causes rhinosinusitis and conjunctivitis in virtually all exposed individuals with lifetime persistence of virus in neural tissues. This latency can result in recrudescent infections throughout the life of an affected cat.

Affected cats reportedly have a history of stress, glucocorticoid administration, or chronic ocular or respiratory disease suggesting this skin disease is associated with reactivation of latent herpes virus infection. However, the respiratory signs may be subtle, and owners should be questioned carefully to determine this facet of the history. The age range of cats reported is between 4 months and 16 years with an average range of 4.5 years. Sex or breed predilections have not been noted, although Ragdoll cats were overrepresented in one report (Burton 2007).

Clinical lesions are striking, but vary greatly in severity. The disease is most commonly charaterised by erosion and ulceration affecting the face and nasal planum. Erythema, swelling, exudation and erosion or ulceration and crusting occur to variable degrees. The dorsal and lateral muzzle, and the periorbital regions are most commonly involved. The planum nasale may be affected. Although most cats have lesions confined to the face, other body regions including distal extremities and the trunk may be affected. Lesions on the distal forelimbs may reflect direct contact during grooming. Lesions may be painful or pruritic.

The clinical differential diagnosis include mosquito bite hypersensitivity, food allergy with facial predominance, pemphigus foliaceus and neoplasia such as squamous cell carcinoma. Previously cats with feline herpesvirus ulcerative dermatitis may have been misdiagnosed as having mosquito bite hypersensitivity or other eosinophilic feline skin diseases. Exacerbation of lesions following corticosteroid or cyclosporin therapy due to erroneous diagnosis, may, in fact, be an important diagnostic clue.

Histopathology shows a marked vesicular and ulcerative eosinophilic infiltrate with amphophilic, intranuclear viral inclusion bodies in the epithelium. Unfortunately, the viral inclusions are not always present. Tissue polymerase chain reaction (PCR) identification of the viral genome has been reported to have a high sensitivity and specificity. Immunohistochemistry for feline herpes virus is also commercially available but is not as sensitive as PCR.

There is only limited information in the veterinary literature regarding the treatment and prognosis of feline herpes dermatitis.

Interferon

Interferon inhibits cellular and viral replication and increases expression of MHC-1 on virally infected cells to increase NK and cytotoxic T cell responses. Clinical resolution with interferon therapy (intralesional and subcutaneous feline recombinant IFN and oral interferon alpha) has been reported however there is a paucity of cases and information on long term follow up. Subcutaneous alpha-interferon (Intron A®: 1 vial contains 3 million units) has appeared beneficial in some cases, sometimes dramatically so. Dosage is approximately 1.5-2 million units/m^2 (a 5 kg cat has a m^2 body area of 0.29 m^2, and thus would receive a dose of 290,000-580,000 units) given subcutaneously three times weekly for at least 6 weeks. Side effects are uncommon but malaise may be seen.

Lysine

L-Lysine is an antagonist for arginine and arginine is essential for FHV-1 replication. Lysine has been shown to decrease viral proteosynthesis. The dose for lysine is 500mg q 12hrs for 30 days abd then q 24hrs for maintenance. Treatment may be required for extended periods. In one report, 5/7 cases reportedly responded to lysine 500mg q 24hrs or lysine 500mg q 24hrs administered in conjunction with interferon alpha 1000IU PO q 24hrs for two days a week (Burton 2007).

Famcyclovir

In a recent study, the systemic anti-herpes drug, famciclovir (Famvir®), was used to treat four cats with FHV-1 associated dermatitis using a dose of 125 mg three times daily for two to six weeks. Famciclovir was well tolerated. All four cats with FHV-1 associated dermatitis improved substantially, although relapse occurred subsequently in three patients. A further cat with presumptive FHV-1 associated dermatitis responded to topical 5% aciclovir cream (Zolaten®) before famciclovir could be sourced (Malik 2009).

Imiquimod

There are recent anecdotal reports of successful outcomes using topical 5% imiquimod cream (Aldara®). Cats generally only tolerate two to three treatments per week, due to irritation reactions. There is an anecdotal report of two cats developing reversible leukopenia following the ingestion via grooming of topically applied imiquimod cream.

Proliferative Necrotising Otitis of Kittens

Proliferative necrotising otitis of kittens is a rare, highly characteristic syndrome of unknown aetiology. The underlying pathogenesis is unknown but as the syndrome bears some resemblance to histopathologically to hyperkeratotic erythema multiforme, an immunologic basis is suspected. Currently there is no evidence to link this syndrome to any infectious viral diseases. Polymerase chain reaction (PCR) testing for feline herpesvirus 1 and papillomavirus immunohistochemistry has been negative.

Lesions develop in kittens between two months and six months of age and regress, apparently spontaneously, by 12 to 24 months.

Clinically, the syndrome is characterised by well demarcated, erythematous plaques with adherent, thick keratinous debris and crusting present on the medial aspect of the pinnae, the entrance to the auditory canal and in some cats the preauricular region of the face. Lesions develop very rapidly and coalesce with erosion and ulceration developing as the lesions progress. Lesions are not usually painful although mild pruritus or discomfort is noted when ulceration in present.

Proliferative necrotizing otitis of kittens is visually distinctive and there are no clinical differential diagnoses. The diagnosis is confirmed by skin biopsy

Histopathology shows a striking parakeratotic hyperkeratosis with marked epidermal and follicular hyperplasia and scattered diffuse, apoptotic keratinocytes.

There is a paucity of literature with regard to treatment of this skin condition. Reportedly the syndrome regresses without treatment. There are anecdotal reports of responses to lysine 250mg q 12hrs, interferon and topical 0.1% tacrolimus ointment.

Bowenoid in situ Carcinoma (Bowen's Disease, Multicentric Papillomavirus-Induced Squamous Cell Carcinoma)

Bowenoid in situ carcinoma (BISC) is a multicentric squamous cell carcinoma in situ of cats, commonly referred to as Bowen's-like disease. It is uncommon and all reported cases have occurred in cats noted to be 10 years of age or older. There is no known sex or breed predisposition.

Lesions usually present as multifocal, heavily crusted plaques and verrucoid lesions occurring in any location of the body. Solitary lesions are seen infrequently. Lesions may occur at any location on the body, but the head is often a target area. Sun-exposed or non sun exposed, pigmented or non pigmented skin may be affected.

Many cases are noted to have papillomavirus (PV) in the affected areas suggesting that PV may be the initiating cause of the lesions. In a recent study, PV was detected by immunohistochemical evaluation in 11 of 23 feline cases (Favrot 2009) supporting the association of PV replication and BISC lesions, however not all BISC samples are positive for PV antigens (Favrot 2009, Wilhelm 2006, Munday 2007) possibly due to the loss of PV protein expression during the malignant transformation process.

Human renal transplant patients develop papilloma virus - associated Bowen's disease due to iatrogenic immunocompromise. Impaired immune surveillance may also be a factor in cats in that 22% of reported cases in cats have been positive for FIV or FeLV (Baar and Helton 1993). A possible localised, viral induced immunosuppression has been suggested by reports of cats with Bowen's disease and concurrent demodicosis where the mites have been retrieved from the follicles within the lesional (Bowenoid) areas only (Guagere 1999).

Histologically, the lesions are characterized by a discrete plaque of moderate to severe, irregular epidermal hyperplasia, marked hyperkeratosis and serocellular crusting. The entire thickness of the epidermis displays dysplastic/ neoplastic keratinocytes but the basement membrane zone is intact. There may be cytopathologic changes to suggest papilloma virus. The breaching of dysplastic/neoplastic keratinocytes through the basement membrane zone into the dermis signals the development of squamous cell carcinoma.

Histologically, the disease must be differentiated from actinic keratosis (early UV light - associated squamous cell carcinoma seen in non pigmented skin). Feline AK presents as plaquelike to papillated, solitary or symmetrical, scaly lesions that occur mostly on the pinnae, nose, and eyelids of white cats attributed to excessive sun exposure. With actinic keratoses (AK), the majority of atypical cells are noted in the basal and lower to mid regions of the epidermis, the epidermis is less hyperplastic, and hair follicles are less deeply affected. Nonetheless, the histologic features are not always conclusive in order to distinguish both diseases, and the pathologist may render a differential diagnosis in such cases. The final diagnosis then has to be made based on clinical features such as the affected area and the colour of the skin/hair coat Immunohistochemistry for papillomavirus may aid in confirming the aetiology.

Therapy for asymptomatic lesions may not be necessary. 90Strontium plesiotherapy (B-irradiation) has been effective in healing thin (less than 2-4 mm) lesions but is not readily available in Australia. CO2 laser therapy can be effective although it may not be curative, especially with more severe disease. However, prolonged remission may be achieved before lesion re-growth warrants repeat of the laser procedure. Sequential laser sessions may be necessary for the management of more severe disease. Oral acitretin (3mg/kg/day) may be effective.

Imiquimod (Aldara) is a topical immune response modifier that has been noted to have both antiviral and anti-tumour effects, through its ability to affect the production of several cytokines and through its enhancement of cell-mediated cytolytic anti-viral activity. In a recent study, 5% imiquimod cream was used in 12 cats with BISC and initial lesions responded to imiquimod 5% cream in all cats. Most cats (75%) developed new lesions. New lesions also responded to imiquimod 5% cream in all cats treated. Five cats (41%) had side effects suspected to be associated with the use of imiquimod 5% cream, including local erythema (25%), increased liver enzymes and neutropenia (8%), and partial anorexia and vomiting (8%) (Gill 2008).

Imiquimod 5% cream appears to be well tolerated in the majority of cats. The author favours using the product three times a week. The frequency of application appears to be directly correlated with the incidence of topical side effects. If irritation is noted, consideration should be given to reducing the frequency of administration. Cats appear to be more sensitive than dogs to the topical side effects of imiquimod.

THERAPIES

New Treatment Options / Regimes For Feline Dermatophytosis

The treatment program must be tailored to the individual patient and will depend on such factors as age, severity of lesions, concurrent diseases and medications, exposure to children and other pets in the environment, previous treatments etc. An important point to recognise is that in an otherwise healthy animal, dermatophytosis is generally a self-curing disease, with full resolution of disease following an adequate cell mediated immune response. Complicated dermatophytosis applies to pets with severe lesions, concurrent diseases and/or a history of previous treatment failure. The website www.giveshelter.org contains useful information on the treatment of dermatophytosis in shelters and other animal care facilities. Treatment will accelerate the resolution of infection, thus minimising the time course of infection and minimizing the spread of infection to other animals and humans.

Clipping The Hair Coat

The value of clipping the hair is to decrease contamination of the environment with infective spores and to make application of topical treatments easier. These factors are especially important for long haired cats, when there are multiple animals in the environment, when the affected pet cannot be segregated and when the lesions are extensive. Cats with fewer than five focal lesions do not need to be clipped. When cats have more than five lesions, long hair and there are multiple pets in the environment and the affected pet cannot be segregated, clipping the entire pet is mandatory. Clipping should be gentle to avoid spreading the infection due to the microtrauma and mechanical spread of the spores. The owner should be warned that a temporary exacerbation of lesions may occur after clipping. Clipping should be performed in a confined area that can thoroughly disinfected by personnel wearing disposable protective clothing.

TOPICAL THERAPY

Spot Therapy

Spot treatment is not recommended even for focal or multifocal lesions because infection beyond the margin of the visible lesions is likely. There is no clinical data to support that the use of spot treatment clear lesions any more rapidly than whole-body treatment alone. If spot treatments are to be used, **terbinafine** (Lamasil ® Novartis) is recommended

Total Body Treatment

Topical therapy inactivates fungal spores and mycelia on and within hair shafts reducing environmental contagion *and* results in a faster mycologic cure than systemic therapy alone. Shampoo therapy, dipping or rinsing with topical antifungal agents is preferred. General topical treatment recommendations are summarised below.

The choice of topical antifungal agent is important because studies have shown that many topical antifungal agents are ineffective. In vitro and in vivo studies have shown that the most consistently effective topical antifungal whole body treatments are **lime sulphur** (not commercially available as a pet product in Australia), **enilconazole**, and **miconazole**; the latter with or without chlorhexidine.

Topical rinses should be continued until a mycologic cure is achieved. A European study compared 2% miconazole, 2% chlorhexidine shampoo (Malaseb ® Dermcare Vet) used with griseofulvin, to griseofulvin treatment alone for dermatophytosis in cats. The cats treated with the shampoo and griseofulvin achieved negative fungal cultures much more rapidly than those treated with griseofulvin alone (Mason 2000).

Systemic Therapy

Systemic therapy is the treatment of choice for dermatophytosis and should be used in all but the mildest uncomplicated cases of dermatophytosis. It is important to remember that systemic antifungal therapy does not rapidly reduce contagion and should be used in conjunction with clipping and topical antifungal agents. Several effective drugs are available, and the appropriate choice should be made depending on cost, fungal species, patient species and potential for toxicity.

Griseofulvin

Griseofulvin is very effective against most of the species of dermatophytes causing infections in cats. Perceived resistance is usually related to incorrect dosing or duration of treatment. Griseofulvin is administered at **50mg/kg PO q 24hrs** or **25mg/kg PO q 12hrs**. The absorption is enhanced when administered as a divided dose and with a fatty meal.

The most common side effects are anorexia, vomiting and diarrhea which can be avoided by dividing or lowering the dose. The drug is highly teratogenic, especially in the first trimester of pregnancy and therefore contraindicated in pregnant animals. Although no teratogenic effects have not been documented after treatment of breeding male cats, griseofulvin can cause abnormalities in spermatozoa in experimental conditions in rodents. It is thus advisable to avoid using recently treated male cats for breeding.

Bone marrow suppression producing anaemia and leukopenia is a relatively uncommon yet severe and unpredictable adverse effect of griseofulvin. These effects can reverse when treatment is withdrawn but irreversible idiosyncratic pancytopenia has been reported. Myelosuppression does not appear to depend on dose, breed or duration of treatment. Severe neutropenic reactions have been reported in cats with dermatophytosis associated with FIV infection. Griseofulvin should not be used in cats with FeLV or FIV. All cats should be tested for FeLV and FIV before griseofulvin is administered. Do not administer to puppies and kittens less than 6 weeks of age.

Itraconazole (ITZ)

Itraconazole (Sporanox ® Jannsen Pharmaceutical) is a very effective fungicidal triazole drug and is indicated for cats that cannot either tolerate griseofulvin therapy or have a resistant strain of *M.canis* infection. The dose in cats is **5mg/kg/day**. ITZ persists in the skin and nails for weeks to months after dosing, and intermittent or pulse therapy is frequently prescribed for skin infections or onychomycosis. In cats a pulse regime has been reported using **5mg/kg/day q 24hrs on alternate weeks for three one week-on and one week-off pulses** and we use this regime in our clinic. Recently a study has been published recommending the optimal treatment for cats in a shelter environment to be itraconazole 10mg/kg/day for 21 days with concurrent 2% lime sulphur treatments twice a week continued until mycological cure (Newbury 2007).

Terbinafine

Terbinafine (Lamisil ®) is a fungicidal allylamine useful in the treatment of superficial dermatophytosis and onychomycosis in humans. Preliminary studies indicate that a dose of 30 to 40mg/kg/day is appropriate for cats. The drug reaches very high concentrations in sebum and stratum corneum and fungicidal concentrations persist in the skin for several weeks after administration in humans. A recent study suggested that after 14 days of treatment in cats at 34 to 46 mg/kg/day, levels of the drug in hair persist above the MIC for *M.canis* for several weeks (Foust 2007). Further studies are needed to determine if terbinafine can be used with pulse therapy regimes in cats. Terbinafine is generally well tolerated; reported adverse effects include vomiting and asymptomatic elevation in liver enzymes. Idiosyncratic acute hepatotoxicity has been reported occasionally. No teratogenicity has been reported.

Lufenuron

Lufenuron (Program Novartis) is a drug that disrupts chitin synthesis which is a component of the outer cell wall of fungi, including dermatophytes. In a retrospective epidemiologic study (Ben Ziony 2000) lufenuron demonstrated a high degree of clinical efficacy in the management of dermatophytosis in dogs and cats. Subsequently, the clinical efficacy has been disappointing and many clinicians have reported treatment failures.

In three separate controlled studies at the University of Wisconsin, using feline experimental infection models, lufenuron at 40 to 100mg/kg once a month seemed to slightly reduce or delay clinical signs, but did not prevent establishment of dermatophyte infections in cats and did not result in a faster cure once the infections were established. In addition, there was no additive effect seen when lufenuron was used along with terbinafine (Moriello 2002, DeBoer 2003).

The drug is not recommended for treatment of dermatophytosis, however a more recent study has suggested that lufenuron at 100mg/kg biweekly for 8 weeks may be an effective pre treatment when combined with other anti-fungal drugs and could possibly be used as an adjuvant in cats with chronic infections unsuccessfully treated with conventional drugs (Mancianti 2008)

Environmental Treatment

The critical role of environmental disinfection in eradication of *M.canis* from an endemic cattery or household cannot be over emphasised. Environmental contamination with *M.canis* spores is widespread, difficult to eliminate and routinely transported by the fur of uninfected cats. Such contamination is a major reservoir for recurrence of infection. *M.canis* spores remain viable in the environment for up to 18 months. Studies using isolated infected hairs or spores or field studies using dermatophyte-contaminated environments have shown that the following disinfectant products are consistently effective: lime sulphur (1:33), enilconazole (0.2%), and 1:10 to 1:100 household bleach. In addition, a study has also shown that strain variation of *M.canis* with respect to susceptibility to disinfectants is not present.

For treatment of routine infections with one or a few animals in the household, extensive environmental decontamination is generally impractical and unnecessary. Thorough vacuuming and mechanical cleaning will remove infective material. All hard surfaces should be mopped with 1:100 bleach solution. During treatment these few animals should be confined to a small easily cleaned room without carpeting until they have received systemic antifungal therapy for at least two weeks and have been dipped at least four times with topical preparations. All bedding, brushes, combs, rugs, cages, carriers are can be washed daily in hot water, detergent and a 1:10 dilution of household bleach

Carpeted areas are problematic because of the lack of effective disinfectant that preserves carpeting. Frequent vacuuming on a daily basis or steam cleaning mechanically removes many but not all spores. To kill fungal spores, the temperature of the water being forced into carpets must be at least 43C (110F). This is not achievable with most of the available machines and therefore steam cleaning may not be a reliable method of killing *M.canis* unless an antifungal disinfectant such as chlorhexidine or sodium hypochlorite is added to the water. Draperies should be dry cleaned and not replaced until the infection is eradicated

CYCLOSPORIN (CSA)

Cyclosporin is an immunosuppressive agent that targets lymphocytes. Particularly important are its effects to suppress IL-2, thus inhibiting activation of CD4$^+$ T-helper cells and the production of other cytokines, such as IL-4, IFN-gamma and granulocyte-macrophage colony-stimulating factor. In veterinary dermatology, cyclosporin is licensed for the treatment of canine atopic dermatitis and as an aid in the management of perianal fistulas. In feline allergy, cyclosporin has been reported to be effective for the treatment of **eosinophilic granuloma complex lesions**, **miliary dermatitis** and **feline atopic dermatitis**. The drug is not currently registered for use in the cat.

Oral cyclosporin appears to be effective for feline allergy at a dose of 5 mg/kg/day. In one study of 10 cats with putative atopy, 5 of the cats experienced a > 50 % reduction in pruritus; 5 cats had lesions improve very significantly or resolve (Noli 2004). In a more recent study, the efficacy of cyclosporin (CsA) was compared with prednisolone for the treatment of feline atopic dermatitis (AD) in a randomised, controlled double blind study. Eleven cats were treated orally with prednisolone (1 mg/kg q 24hrs) and 18 were treated with CsA (5 mg/kg/day) for 4 weeks. There was no significant difference between the two treatment groups (Wisselink 2009).

CsA is used effectively to manage feline eosinophilic skin diseases including eosinophilic granuloma, eosinophilic plaque, indolent ulcer and/or linear granuloma at a dose of 5 to 10mg PO q 24hrs for 4 weeks reducing to q 48hrs for 1 to 2 months until remission of symptoms and then twice a week for an unlimited duration (Vercelli 2006) although eosinophilic ulcers seem less responsive to treatment (Guagere 2000)

Few adverse reactions to CsA have been reported in cats. Reported side effects include anorexia, vomiting, intermittent soft faeces, salivation, head shaking and gingival hyperplasia. Diarrhea has been most frequently noted. In one study, capsules caused diarrhea whereas the same dose administered as liquid formulation did not produce any adverse reaction (Vercelli 2006). It is possible that an excipient of the capsules was responsible for this gastro-intestinal disorder.

It is important to be aware that acute fatal toxoplasmosis has been reported in cats associated with CsA treatment for feline atopy (Beatty 2003, Last 2004). Various experimental studies have shown that the immunosuppressive effects of CsA may alter the natural course of *T. gondii* infection with increased severity of lesions, persistence of parasites in visceral locations and down-regulation of the host–parasite interaction all being reported. Predisposition to recrudescent flare-ups of chronic *T. gondii* infection, in addition to the development of acute systemic disease following acquired infection, might also occur in cats on CsA therapy.

Precautions to consider during immunomodulatory therapy would include feeding only commercial cat food or other cooked foods, avoiding feeding of raw meat, poultry, viscera or bones and preventing hunting and scavenging. Monitoring of serological antibody status, for both IgG and IgM class antibodies to *T. gondii*, both prior to initiation of immunomodulatory therapy, as well as during immunosuppressive therapy, might be helpful to detect seroconversion. When seroconversion occurs, or significant rises in toxoplasma antibody titres are observed in association with developing clinical illness in cats which were seropositive prior to initiation of immunosuppressive treatment, antitoxoplasma chemotherapy with clindamycin should be applied immediately to prevent acute systemic toxoplasmosis. It is also advisable to test for FIV and FelV even though no clinical expression of the viral disease was observed in two FIV positive cats treated with cyclosporin (Vercelli 2006)

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Chapter 28

Update on Nontuberculous Mycobacterial Syndromes in Cats And Dogs

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FELINE PANNICULITIS DUE TO RAPIDLY GROWING MYCOBACTERIA

Rapidly growing mycobacteria (RGM) are a heterogeneous group of organisms that produce colonies on synthetic media within seven-days when cultured at 24°C to 45°C. They are distributed ubiquitously in nature. RGM include the *M fortuitum* group (including *M fortuitum*, *M peregrinum*), the *M chelonae/abscessus* group (including *M chelonae* and *M abscessus*), the *M smegmatis* group (including *M smegmatis* sensu stricto, *M goodii* and *M wolinkskyi*) and a variety of other species. The taxonomy of this group has been revised recently and because of this, the word 'group' is used when referring to isolates recorded in early publications. RGM are strongly linked with localized infections of immunocompetent hosts. This is because they are well adapted to a saprophytic existence and inherently have low virulence. Thus, they do not produce disease unless a breakdown in normal defense barriers provides them with a portal of entry to a favorable tissue environment. Once introduced, RGM are generally constrained by a vigorous immune response that may or may not eradicate them, but is effective enough to prevent haematogenous or lymphatic spread. RGM can produce widely disseminated disease, but only in severely immunocompromised individuals.

Mycobacterial panniculitis refers to a syndrome characterized by chronic infection of the subcutis and skin with RGM. This condition is quite common in cats, especially in Australia. It is seen less commonly in dogs, and also in Australian native animals such as Quolls and Tasmanian Devils. RGM replicate in mammalian tissues when introduced through some break in the skin. This typically follows penetrating injury, especially when the wound is contaminated by dirt or soil. Preference of RGM for fat is a key factor in the pathogenesis and results in a tendency for disease to occur in obese individuals and in tissues rich in lipid, such as the subcutaneous panniculus and especially the inguinal fat pad. Experimental infections cannot be induced in cats that do not have appreciable subcutaneous fat. Adipose tissue offers a favorable environment for survival and proliferation of RGM by providing triglycerides for growth or protecting organisms from the phagocytic and immune responses of the host. Initial reports suggested mycobacterial panniculitis was more common in warm humid climates; however cats from temperate regions, including parts of Australia, Canada, Finland and Germany, have subsequently been reported. In Australia, the *M smegmatis* group accounts for the majority of feline cases, whereas it is a much less common cause of equivalent infections in human patients.

Clinical Signs

Infections tend to start in the inguinal region, usually following contamination of cat fight injuries, e.g. raking wounds inflicted with the hind claws. The infection may spread to contiguous subcutaneous tissues of the ventral and lateral abdominal wall and perineum. Penetrating injury by sticks, metallic objects and vehicular trauma may also give rise to these infections, as can cat and dog bite injuries contaminated with soil or dirt. Sometimes infections start in the axillae, flanks or dorsum.

Early in their course, infections resemble catfight abscesses, but without the characteristic fetid odor and turbid pus. Instead, a circumscribed plaque or nodule is apparent. Later, there is progressive thickening of the nearby subcutis to which overlying skin becomes adherent. Affected areas become denuded of hair and numerous punctate fistulae appear, discharging watery exudate. Fistulae are intermingled with focal purple depressions (thinning of the epidermis over accumulations of pus). The 'lesion' gradually increases in area and depth, and may eventually involve the entire ventral abdomen, adjacent flanks or limbs. If cats are presented promptly for veterinary attention and the lesion confused with an anaerobic cat-bite abscess, surgical drainage and administration of a β-lactam is typically followed by wound breakdown and development of a non-healing suppurating tract surrounded by indurated granulation tissue. Some affected cats with infections develop systemic signs, becoming depressed, pyretic, inappetent, losing weight and being reluctant to move. Occasional cats develop the hypercalcaemia of granulomatous disease, although this is rarely symptomatic. Surprisingly, other cats remain comparatively well despite extensive disease. Usually the problem remains localized to the skin and subcutis. Although adjacent structures such as the abdominal wall can be affected eventually, spread to internal organs or lymph nodes is very unusual.

Diagnosis

Sample Collection, Cytology and Histology

A tentative diagnosis of mycobacteriosis can be confirmed by collection of pus or deep tissue specimens. This material is used to confirm the diagnosis using appropriately stained smears, histological sections and culture. A histological diagnosis is unnecessary if appropriate samples for cytology and culture have been procured. It is vital to give the laboratory warning that mycobacterial aetiology is suspected so special procedures for processing can be adopted.

In our experience, samples of pus obtained from needle aspirates of affected tissues through intact skin provide the best laboratory specimens. This material can be obtained from a palpably abnormal portion of the subcutis. The overlying skin should be carefully disinfected with 70% ethanol prior to obtaining the specimen to preclude the isolation of saprophytic mycobacteria from the skin surface. It may be necessary to carefully move the needle in the subcutaneous space, while applying constant negative pressure, until a pocket of purulent material is encountered. Aspirated fluid should be submitted for cytology and mycobacterial culture, or inoculated immediately into a commercially prepared mycobacteria culture bottle that is subsequently submitted to the laboratory. It is only necessary to suck a small amount of liquid material into the hub of the syringe. It is easiest to submit the entire syringe to the laboratory after replacing the needle with a sterile cover. Exudate from draining sinus tracts is heavily contaminated secondary invaders and represents an inferior sample. If deep biopsies are obtained, they should be triturated in brain heart infusion broth using a sterile mortar and pestle to produce a tissue homogenate suitable for cytology and culture.

Smears prepared from aspirates or tissue homogenates should be stained using Diff Quik®, Gram stain and a modified acid-fast procedure (decolorizing with 5% sulphuric acid for only three to five minutes; RGM are *not* as acid-fast as other mycobacteria). Cytology invariably demonstrates pyogranulomatous inflammation and it is generally possible to visualize Gram positive and/or acid-fast bacilli (AFB) in smears, although an exhaustive search may be required. Histologically, there is pyogranulomatous inflammation. AFB may be hard or impossible to find in Ziehl-Nielsen (ZN) stained tissue sections and are often located in lipid vacuoles. Some US dermatologists favour Fite's stain for detecting AFB in tissues.

Bacteriology and Antimicrobial Susceptibility Testing

Tissue homogenates and pus should be streaked onto blood agar plates and a mycobacterial medium such as Lowenstein-Jensen medium or 1% Ogawa egg yolk medium and incubated aerobically at 37°C and 25°C. If available, the BACTEC system can also be utilized. Moderate to heavy growth of pinpoint, non-hemolytic colonies is usually detected after 2-3 days (occasionally longer) on sheep blood agar at 37°C. A useful method which can be used to differentiate RGM from contaminant flora is by primary isolation around antibiotic sensitivity discs (first generation cephalosporins or isoxazolyl penicillins) applied to the plate after inoculation.

There is great value in determining species identification and susceptibility data in every case, as this has a big impact on antimicrobial strategies. Species identification can be carried out in a well equipped veterinary bacteriology laboratory although it if often more convenient to send the strain to a Mycobacteria Reference Laboratory following primary isolation. Identification takes into account a number of phenotypic and biochemical features. Minimum inhibitory concentrations (MICs) for ciprofloxacin, moxifloxacin, gentamicin, trimethoprim, clarithromycin and doxycycline can be determined easily using the Etest (AB Biodisk, Solna, Sweden) method. This methodology is less demanding than the 'gold standard' of broth microdilution. Antimicrobial susceptibility of clinical isolates can also be determined using disc diffusion methodology.

Therapy

The management of feline mycobacterial panniculitis continues to evolve in the light of clinical experience, availability of new anti-infective agents and the development of new surgical techniques. There is great variation in the severity and extent of lesions from patient to patient. Difficulty in making a prompt diagnosis is partly responsible for the chronicity, severity and refractoriness of these infections. Briefly, treatment should commence with oral antimicrobial(s) (doxycycline, a flouroquinolone and/or clarithromycin), initially chosen empirically, but subsequently based on *in vitro* susceptibility data. Sometimes long-term administration of such an agent or agents is sufficient to effect a cure, but in many severe cases it is eventually necessary to surgically resect recalcitrant tissues so that oral antimicrobial therapy will be able to cure the infection permanently. Given the extent and severity of the pathology in many of these cases, it is understandable that adequate levels of antimicrobials may not be achieved throughout all affected tissues and that in these cases the best chance for a successful outcome is to remove as much infected tissue as possible following preliminary drug therapy. Residual foci of infection can then be targeted by high concentrations of antibiotics achieved during and after surgery. Peri- and post-operative antimicrobial therapy is vital to ensure primary intention healing of the surgical incision. In the future, drugs such as moxifloxacin and pradofloxacin may prove even more effective that agents currently available.

Ideally, the choice of antimicrobial should be based on culture and susceptibility testing. For empiric therapy, a combination of doxycycline (5 mg/kg orally twice daily using the monohydrate salt, or even higher doses if tolerated) plus moxifloxacin (10 mg/kg orally once a day compounded) will successfully treat most cases. Clarithromycin is very effective for *M fortuitum* and *M chelonae/abscessus*, but does not work for over 70% cases with *M smegmatis* group infections. In my view, enrofloxacin is relatively contraindicated in these cases because of the need for higher than routine doses and long courses, which amplify the risk of retinotoxicity; the new Bayer drug pradofloxacin will be safer and far more effective than Baytril in this setting.

DISSEMINATED *MYCOBACTERIUM AVIUM-INTRACELLULARE* COMPLEX (MAC) INFECTION IN YOUNG CATS WITH A PUTATIVE CELL MEDIATED IMMUNODEFICIENCY SYNDROME

We have reported a new syndrome of disseminated MAC infection in ten young cats (1 to 5 years-of-age) from Australia or North America. A further two cats with disseminated mycobacteriosis (precise agent not identified) were recognised also. Of the twelve, ten were Abyssinian cats, one was a Somali cat and one was a domestic shorthair cat. None of the cats tested positive for either FeLV antigen or FIV antibody.

The clinical course of these infections was indolent, with cats typically presenting for weight loss, initially in the face of polyphagia, with a chronicity of up to several months. Additional clinical features included lower respiratory tract signs and peripheral lymphadenomegaly. A marked diffuse interstitial pattern was evident in thoracic radiographs, even in cats without overt respiratory involvement. Hair clipped to perform diagnostic procedures tended to regrow slowly, if at all. Diagnosis was generally made by obtaining representative tissue specimens from mesenteric lymph nodes, liver or kidney at laparotomy, or from a popliteal lymph node. The primary antecedent event was most likely colonisation of either the alimentary or respiratory tract, followed by local invasion and eventual lymphatic and haematogenous dissemination.

Nine cases were treated using combination therapy with agents effective for MAC infection in human patients. The results were generally favourable, although the disease had a tendency to recur if insufficient treatment courses were utilised. Cats were generally treated with long courses (5 to 14 months) of clarithromycin combined with either clofazimine or rifampicin, and a fluoroquinolone or doxycycline was sometimes given also, although in the future moxifloxacin may prove to be a superior adjunctive agent in this setting.

Certain lines of Abyssinian and Somali cats likely suffer from a familial immunodeficiency that predisposes them to infection with slow-growing mycobacteria such as MAC. Studies of this problem are on-going.

FELINE LEPROSY SYNDROMES

Historical Perspective

The term feline leprosy is used to refer to a disease in which single or multiple granulomas form in the skin or subcutis in association with large numbers of acid-fast bacilli (AFB) which are nonculturable using standard methods. The condition was first recorded in the literature by Australian and New Zealand researchers in the early 1960s. Since then, the disease has been reported in Western Canada, the Netherlands, France, the UK and USA.

Historically, the causative agent of feline leprosy was purported to be *Mycobacterium lepraemurium*. This bacterium causes murine leprosy, a systemic tuberculosis-like infection of rats. Cats are thought to contract *M lepraemurium* following bite injuries from infected rodents. *M lepraemurium* is a fastidious, slow-growing organism which, with difficulty, can be cultured from large inoculae on Ogawa’s egg yolk medium under special conditions. Although a few investigators have successfully grown *M lepraemurium* from infected cats, the basis of ascribing this bacterium as the etiological agent of feline leprosy was dependent on transmission studies. Interestingly, some cats appeared much more susceptible to experimental infection than others.

According to the literature, cats with feline leprosy are typically young adults (< 5 years-of-age), perhaps with a preponderance of males. Presumably these patient characteristics reflect the need for the cat to interact with a rat to become infected. The initial lesion is a focal granuloma of the subcutis. Owners become aware of solitary, or more commonly multiple, painless, raised, fleshy, tumor-like lesions, from a few millimeters up to 4 cm in diameter. These granulomas are freely movable over underlying tissues. Lesions can develop rapidly and when large, may ulcerate. Infection spreads to adjacent areas and may invade underlying tissues and drain to regional lymph nodes. Lesions can occur anywhere, but tend to be concentrated on the head and limbs. Small lesions are occasionally found on the tongue, lips and nasal plane. Lesions, even if multiple, tend to be initially concentrated in one region and have the propensity to recur following excision.

Pathologically, feline leprosy was subdivided into lepromatous or tuberculoid forms based on the no. of AFB present (multibacillary *v* paucibacillary) and the host immunological response (lepromatous *v* tuberculoid). Because the causal mycobacteria are slow-growing organisms capable of intracellular survival, the histologic picture actually depends on the host's immune response. When this response is poor, lepromatous (multibacillary) disease develops with infiltration of the dermis with large sheets of 'incompetent' foamy macrophages containing enormous numbers of organisms. AFB are usually arranged in the cytoplasm of macrophages as dense parallel accumulations which displace the nucleus to an eccentric position. Lymphoid cells and plasma cells are virtually absent from the lesions. If the host's immune response is more effective, histiocytic cells are accompanied by moderate numbers of lymphoid cells and plasma cells and multiplication of the organism is limited - the so-called tuberculoid response.

AFB in smears and tissue sections appear as long slender rods. In smears stained with Romanowsky stains such as DiffQuik or Geimsa, organisms appear as negative-staining bacilli. In smears or sections stained with modified acid-fast stains such as ZN or Fite's stain, organisms take up the carbol fuschin and are acid/alcohol fast.

Molecular Insights

Molecular methodologies have been used to investigate presumptive feline leprosy. Of eight cases of invasive or disseminated cutaneous mycobacterial disease investigated by Siobhan Hughes and colleagues using material collected largely from New Zealand cats, four were shown to have *M lepraemurium* infections. Of the remaining cases, one cat had a disseminated *M avium* infection, the aetiology in one cat was undetermined and in two cases infection was attributable to a novel mycobacterial species. This information encouraged a reappraisal of Australian feline leprosy cases, and subsequently this work has been extended to North America by groups lead by Greg Appleyard and Janet Foley.

In Australia, cats were initially be divided into two groups based on the patients' age, lesion histology, clinical course and sequence of 16S rRNA PCR amplicons obtained from lesions. More recently, we have identified a new cohort of Australian cats from the Gippsland region of Victoria which were infected by a third novel mycobacterial species.

1. The first group consisted of young cats (typically < 4-years) which initially developed localised nodular disease affecting the limbs. Lesions progressed rapidly and sometimes ulcerated. Sparse to moderate numbers of AFB were identified using cytology or histology, typically in areas of caseous necrosis and surrounded by tuberculoid inflammation. Organisms did not stain with haematoxylin and ranged from 2-6 µm (usually 2-4 µm). *M lepraemurium* was diagnosed based on the sequence of a 446 bp fragment encompassing the V2 and V3 hypervariable regions amplified from lesions using PCR and mycobacterial primers.
2. The second group consisted of old cats (>9-years) with generalised nodular skin lesions associated with multibacillary lepromatous histology. Some cats initially had localised disease that subsequently became widespread, while others had generalised disease from the outset. Disease progression was protracted, typically taking months to years, and skin nodules did not ulcerate. Microscopically, lesions consisted of sheets of epithelioid macrophages containing large to enormous numbers of AFB 2-8 µm (mostly 4-6µm) which stained also with haematoxylin. A single unique sequence spanning a 557 bp fragment of the 16S rRNA gene was identified in lesions from these patients. The sequence was characterized by a long helix 18 in the V3 region, suggesting the new species was likely to be a fastidious, slow-grower. The 16S rRNA sequence had greatest nucleotide identity with *M leprae*, *M haemophilum* and *M malmoense,* and contained an additional 'A' nucleotide at position 105 (the only other mycobacterial database sequence with the same extra nucleotide being *M leprae*). A very slow, pure growth of a mycobacterium species was observed on Lowenstein-Jensen medium (supplemented with iron) and semisolid agar in one case. The environmental niche of this new mycobacterium species has yet to be determined, although

the preponderance of cases from rural or semi-rural areas of coastal NSW suggests it is a saprophyte found more commonly in these locations than in metropolitan environments.

3. The third group consisted of 12 cats, typically young adults (2 to 8 years), with lesions located on the head, cornea, conjunctiva or distal limbs, and lesions that were generally multibacillary and lepromatous. The remarkable finding was that, with one exception, cases were encountered in a very restricted part of rural Victoria. The distribution of lesions is most compatible with a saprophytic organism being inoculated in tissues subsequent to cat scratch injuries.

The presence of tuberculoid pathology is generally marker of disease in an immune-competent host and such infections are often initially localised. In contradistinction, the presence of a foamy histiocytic infiltrate of the dermis and subcutis in patients with mycobacteriosis is observed almost exclusively in association with profound immunodeficiency, such as that seen with terminal HIV infection in human patients. Widespread dissemination of infection (rather than local invasion) suggests decreased immunological surveillance permits the development of disease with an organism usually considered to have limited virulence. Feline leprosy caused by the novel NSW mycobacterial species, the Victorian novel species or more rarely *M lepraemurium*, may likewise represent a manifestation of deteriorating immune competence.

For epidemiologic reasons, feline leprosy in young cats is almost invariably caused by *M lepraemurium,* the novel NSW species is almost invariably seen in old (likely immunosuppressed cats) while the novel Victorian species can occur in either immune competent or immune defective cats.

To make matters even more complex, recent work by Appleyard and colleagues has demonstrated a third mycobacterial syndrome in cats from western Canada and the USA (Idaho and Oregon) called ‘feline multisystemic granulomatous mycobacteriosis’. This disease is caused by a slow-growing taxa provisionally called *M visible*. This species is capable of producing widespread dissemination to multiple internal organs, presumably in immune deficient cats. Sequence analyses demonstrate a number of nucleotide differences between *M visibile* and both *M lepraemurium* and the novel species reported by Hughes et al.

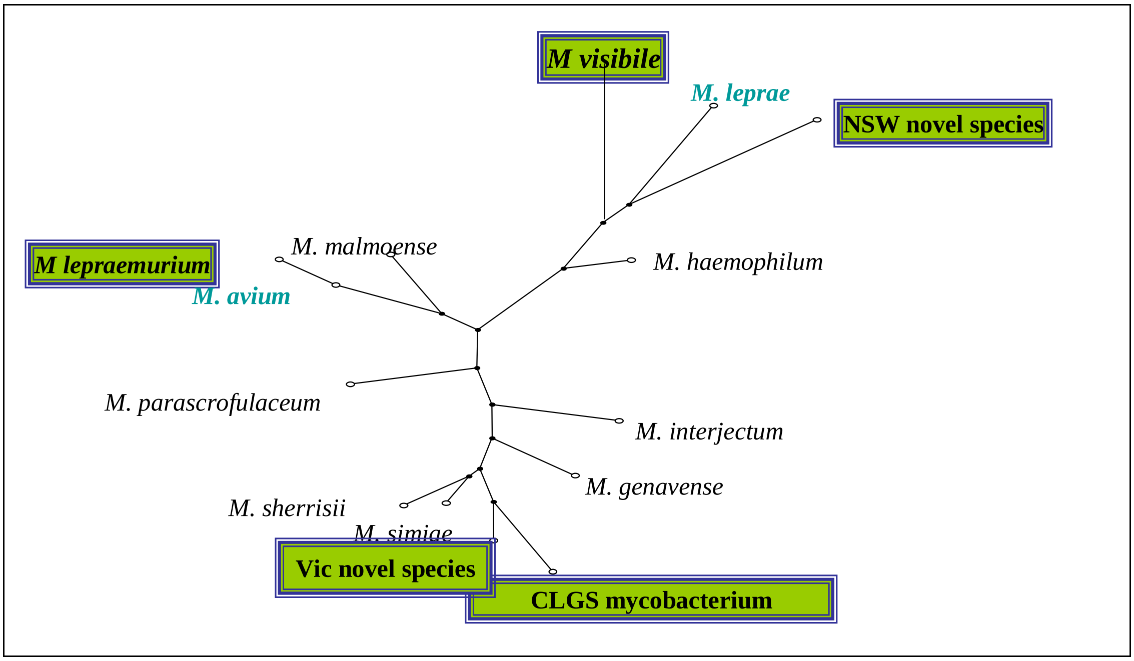

Image 28.1. Unrooted phylogenetic tree of selected *Mycobacterium* species computed from concatenation of 16S rRNA gene, ITS and hsp65 sequences by maximum likelihood.

Diagnosis

Diagnosis of the 'feline leprosy' syndromes is usually straightforward, provided that the clinician has a high index of suspicion for the condition. Needle aspirates, crush preparations of biopsy material and histological sections stained with ZN or similar methods contain easily demonstrable AFB surrounded by variable granulomatous to pyogranulomatous inflammation. In DiffQuik stained smears, mycobacteria can be recognized by their characteristic 'negative-staining' appearance and location within macrophages and giant cells.

Material should be submitted also for culture, because occasionally slowly-growing species such as MAC and *M genavense* and the tubercle bacillus (*M bovis* or *M microti*) can produce an identical clinical presentation; in such cases optimal antimycobacterial therapy can be selected more readily on the basis of *in vitro* susceptibility results and information available in the literature. In the majority of cases, however, conventional mycobacterial culture is negative due to the fastidious nature of the causal organisms and the exact aetiology can only be proven using PCR amplification and sequence determination of gene fragments. PCR has the additional advantage of providing a rapid diagnosis. Fresh (frozen) tissue delivered to a mycobacterium laboratory with PCR facilities provides the optimal sample, although freeze-dried specimens may be more conveniently sent where tissues need to travel long distances. Sometimes PCR can be performed successfully on formalin-fixed paraffin-embedded material, although fixation conditions invariably cause some DNA degradation which may limit the success of the procedure. Recently, Hughes and colleagues have developed specific PCR assays to diagnose infections due to *M lepraemurium* and the novel species; furthermore, use of a simple restriction enzyme digest allows these assays to distinguish *M visibilis* strains also.

Therapy

Too few cases with a documented aetiology have been reported to provide definitive treatment guidelines. Although *M lepraemurium* and the novel species can be cultured *in vitro with difficulty*, it is currently not routine or reliable to isolate these organisms due to their slow growth and fastidious requirements. Determination of *in vitro* susceptibility data for individual isolates is therefore not possible.

Only limited experimental studies have been undertaken to determine effective drug therapy for *M lepraemurium in vitro* or *in vivo* and as yet we have limited data only for the novel mycobacterial species. Portaels and colleagues found the minimum inhibitory concentration for rifampicin of two strains of *M lepraemurium* to be 4 and 8 µg/mL, levels that should be just obtainable *in vivo*. Other drugs shown to have activity against *M lepraemurium in vitro* include ansamycin compounds (rifabutin) and sulpha drugs. There is a good deal of clinical evidence that clofazimine has efficacy *in vivo*, while it is likely that clarithromycin would be also be effective based on its wide spectrum of activity against slow-growing mycobacterial species.

The literature suggests that when *M lepraemurium* infection is diagnosed early, while disease is localized, wide surgical excision of infected tissues provides the best chance to simply and rapidly effect a cure. Aggressive resection techniques should be adopted, with *en bloc* resection of all lesions, and reconstruction of resulting tissue deficits using appropriate surgical techniques. Such an approach should be combined with adjunct antimicrobial therapy beginning a few days prior to surgery, so that effective levels of drugs are present in blood and tissues intra- and postoperatively to ensure primary intention healing. Clofazimine (at a dose of up to 10 mg/kg once daily orally; typically 25 to 50 mg every 24 to 48 hours – available thru BOVA Compounding Pharmacy) has the best reported success rate, although it is likely that combination therapy using two or more drugs will eventually prove superior. Drugs that could be combined with clofazimine include rifampicin and clarithromycin, although sulpha drugs, doxycycline, new fluoroquinolones such as moxifloxacin or pradofloxacin, or amikacin may in time also prove to be useful.

In feline leprosy cases caused by novel mycobacterium species, we believe combination therapy using two or three of clofazimine (25 to 50 mg per cat orally every day or every other day), clarithromycin (62.5 mg twice daily) or rifampicin (10 to 15 mg/kg per day) represents optimal therapy. However we are currently unsure of which will prove to be the best combination, and side effects in individual cats may affect which two drugs are used in a given patient. Currently, we recommend a combination of rifampicin and clarithromycin as initial therapy. The new quinolone moxifloxacin may prove useful in future cases, as it has good antimycobacterial activity and is affordable. Other new agents such as linezolid may also have a place, although currently they are prohibitively expensive for most owners.

CANINE LEPROID GRANULOMA SYNDROME “CANINE LEPROSY”

Canine leproid granuloma syndrome (CLGS), or canine leprosy, is the most common mycobacterial disease of dogs in Australia. Although the causal organism has a worldwide distribution, its prevalence in other countries has not been documented. Patients with this infection present with one or more nodules in their subcutis or skin, but are otherwise well.1-7 The condition was first described in a Boxer and a Bullmastiff from Zimbabwe in 1973, with similar reports from Australia appearing soon afterwards.

Primary skin lesions consist of single or multiple, well circumscribed nodule(s). These lesions can appear anywhere on the dog, although usually they are located on the head and typically on the dorsal fold of the ears. The nodules are hard, painless, and vary in size from 2 mm up to 5 cm in diameter. Small nodules are detected as hard subcutaneous lumps, while larger nodules may show superficial hair loss. Very large lesions may ulcerate.

Leproid granulomas are confined to the subcutis and skin and do not involve regional lymph nodes, nerves or internal organs. Consequently, affected dogs suffer no apparent systemic ill effects. This suggests that the causal organism has low pathogenicity or special prerequisites, such as a requirement for low temperature, which permits them to survive and multiply in superficial tissues only. Lesions can be disfiguring and cause irritation, especially when lesions are multiple and secondarily infected with *Staphylococcus intermedius*.

CLGS has a wide geographic distribution, with cases recorded from coastal and inland regions of all states of Australia. The causal organism is likely to have a world-wide distribution, as the condition has also been reported in New Zealand, Zimbabwe, Brazil, California and Florida. The authors are also aware of unreported cases of affected Boxers in New York state and Foxhounds in Georgia, USA. The condition would seem to be especially common in Australia and Brazil.

Interestingly, there is a strong propensity for short-coated breeds to be affected, with Boxer and Boxer-cross dogs accounting for nearly half of the cases reported. Despite the fact that CLGS was first reported nearly 30 years ago, its aetiopathogenesis has not been fully elucidated. The initial report of the disease by Richard Smith stated 'lesions appear suddenly, and are usually seen on dogs pestered by biting flies'. This might suggest that flies, or some other biting arthropod (such as midges or mosquitoes), inoculate mycobacteria from an environmental niche into susceptible tissues. The predilection for lesions to develop in regions favoured by biting insect vectors, such as the head and particularly the ears, is consistent with this hypothesis, as is the overrepresentation of short-coated, large breed dogs (which are generally housed outdoors).

Diagnosis

Diagnosis is usually straightforward as the distribution of lesions (especially the propensity for the dorsal ear fold to be affected), coupled with the tendency for lesions to be multiple, particularly in an at-risk breed, is strongly suggestive of CLGS. Diagnosis can be confirmed by obtaining specimens of representative lesions for cytologic or histologic examination. DiffQuik-stained smears from needle aspirates typically demonstrate numerous macrophages with variable numbers of lymphocytes and plasma cells and lower numbers of neutrophils. Usually few-to-moderate numbers of negatively-stained, medium-length bacilli can be detected within macrophages or extracellularly. Histologically, lesions within the subcutis and dermis consist of pyogranulomas composed chiefly of epithelioid macrophages, Langerhans-type giant cells with scattered neutrophils, plasma cells and small lymphocytes. The number and morphology of acid fast bacilli (AFB) in Ziehl-Neelsen-stained section is highly variable from case to case. Currently, it is impossible to confirm the diagnosis by culture, as the in vitro growth requirements for this fastidious organism have not been determined. A negative culture, however, can exclude other mycobacterial aetiologies. It is vital to thoroughly disinfect the skin surface prior to obtaining specimens for culture, as saprophytic mycobacteria can easily be cultured erroneously from dirt present on canine skin.

PCR methodologies using ‘universal primers’ designed to amplify regions of the bacterial 16S rRNA gene have been performed on leproid granuloma specimens from dogs. Using sequence capture PCR for paraffin-embedded specimens and nested PCR on DNA from fresh tissue specimens, a novel PCR product has been identified with identical sequence over a 350 bp region. Analysis of the partial 16S rRNA sequence supports the notion that the novel species is a fastidious, slow-growing mycobacterium. In total, molecular methodologies identified this proposed novel mycobacterial sequence in material from in excess of 25 Australian cases of CLGS indicating that the species represented by this sequence is probably the principal causative agent of CLGS. Our continuing experience, and those of colleagues in California and Brazil, supports this contention. Interestingly, the species represented by this sequence has never been recorded from mycobacterial granulomas affecting the skin or subcutis of cats, horses, people, or other non-canine mammalian species. Hence, there is thought to be no public health risk to the owners of affected dogs.

Treatment

Very little has been written concerning the treatment of CLGS. Many cases are self-limiting, with the nodular skin lesions regressing spontaneously with time, typically within 1 to 3 months of appearing. The stated time frame is based on our experiences consulting with veterinarians in relation to cases diagnosed histologically; by the time the sections are submitted, processed, reported on and we establish a dialogue with the clinician, lesions are often already starting to regress, either spontaneously, or in response to antimicrobials (useful for secondary Staphylococcus intermedius, but with unlikely efficacy for mycobacteria). This ‘self cure’ occurs presumably as a result of an effective cell-mediated immune response mounted by the patient.

In cases with a limited number of lesions, surgical excision can be curative and provides material with which to confirm the diagnosis histologically and using PCR. In other cases, however, the infection progresses to produce chronic, disfiguring lesions that may persist indefinitely. Limited information suggests that treatment with conventional antimicrobial regimens using β-lactam drugs or doxycycline (as monotherapy) fails to have a significant impact on the course of infection, although these drugs may be of some benefit by effectively treating secondary pyogenic infections. One report concerning two dogs from Brazil suggested topical antibacterial treatment and orally administered rifampicin may be effective. Our experience treating ‘canine leprosy’ suggests that this infection responds to therapy with combinations of antimicrobial agents known to be effective against nontuberculous mycobacteria, including rifampicin, clarithromycin, clofazimine and doxycycline. Based on our evolving experience, a combination of rifampicin (10 to 15 mg/kg PO every 24 h) and clarithromycin (15 to 25 mg/kg PO total daily dose; divided and given every 8 to 12 h) is currently recommended for treating severe or refractory CLGS cases. Unfortunately, the clarithromycin component of therapy is, at present, extremely expensive in large dogs. A far more affordable combination consists of rifampicin (at the same dose) and doxycycline (5 mg/kg or higher every 12 hours), and further studies may prove this to have similar efficacy to the former regimen. Treatment should be continued until lesions are substantially reduced in size (typically for 4 to 8 weeks) and ideally until lesions have resolved completely. It is prudent to monitor hepatic function periodically during treatment, as rifampicin may cause hepatotoxicity in some patients. A topical formulation containing clofazimine in petroleum jelly may be used as an adjunct to systemic drug therapy. This can be prepared by crushing (with a hammer) 40 50mg clofazimine ‘capsules’ within a plastic bag; the extracted liquid dye is mixed into an ointment with 100 gm petroleum jelly. Further work is required to determine the most cost effective treatment regimen for this condition, and to this end a topical treatment using multiple chemotherapeutic agents in a permeant vehicle is currently under development in Australia.

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Feline Leprosy

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Chapter 29

Update on Canine Demodicosis

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AETIOLOGY

Demodex canis is an obligate parasite of the dog (though experimentally *D. canis* can infest hamster skin grafted onto a mouse model) and low numbers of mites are part of the normal cutaneous fauna. *D. canis* mites are transmitted from the bitch to nursing puppies within a few days of birth and have not been found on stillborn puppies or puppies delivered by caesarean. Under the effects of poorly defined genetic or immunologic changes, or concurrent disease or immunosuppressive drug use, the population can markedly increase leading to disease. Transmission of clinical disease from affected to healthy dogs has not been demonstrated except for one study. *D. canis* is the most commonly reported demodecid mite in both normal and diseased dogs, however two other *Demodex* spp. mites have also been recognised in the dog.

D. injai is a long-bodied mite that has been histologically identified in hair follicles and sebaceous glands. This long-bodied mite is characterized by a longer body (334-368μm compared with 167-244μm in *D. canis*), a longer ophisthomal length (225-258μm compared with 91-115μm) and an absence of the ophisthomal organ in the male (which is present in *D. canis*). Short-bodied demodex mites (unnamed) have also been recognised and are thought to inhabit superficial keratin. They are only uncommonly identified as a sole presentation and most commonly are found as part of a *D. canis* infestation. These latter two variants are not uncommon in Melbourne.

Recently though, the whole taxonomy of canine *Demodex* spp. has been questioned with one report suggesting that all species are in fact morphological variants of *D. canis* depending on location in the skin and anatomical location. DNA studies of the different morphological forms (sequencing of *D. canis* has been performed already) should definitively answer this question.

CLASSIFICATION AND CAUSES

Canine *D. canis* demodicosis is classified according to the patient's age at the onset of disease, and this relates to the probable underlying triggers for the disease.

Juvenile-onset demodicosis typically occurs in dogs less than 18-36 months of age. Juvenile-onset demodicosis is further categorised as localised or generalised according to the extent of the disease. A variety of opinions exist on defining localised vs. generalised demodicosis (and this ultimately affects the approach to treatment) but consideration should be given to treating a case as generalised when the condition:

- involves the feet
- affects an entire body region
- affects 4-5 or more separate sites
- is rapidly spreading, especially in a predisposed breed
- has persisted for 4-6 months with no sign of resolution.

The exact trigger for clinical canine demodicosis is unknown but is suspected to be secondary to immune system dysfunction. Genetics have been shown to play a significant role in disease development, and oestrus has also been reported a risk factor. Recently, a major epidemiological study in the US conducted at 600 hospitals and involving the records of almost 1.2 million dogs has shed some objective light on disease and breed associations with juvenile-onset generalised demodicosis. Poor body condition appeared to be significantly associated with demodicosis with Staffordshire bull terriers, bull terriers, French bulldogs, Shar Peis, American Staffordshire bull terriers, pit bulls, English bulldogs, boxers, American bulldogs, miniature Pinschers, Great Danes and Pugs identified as significantly at-risk breeds. While these at-risk breeds are very familiar even here in Australia it is heartening that the breeds identified as significantly at risk has moved from the subjective opinion of some authors to information grounded in statistics. Interestingly, the same study showed a higher risk in the hot, humid south-western states of the US, raising the possibility that climatic conditions may also favour development of the disease.

Adult-onset demodicosis is often associated with systemic diseases (e.g. hyperadrenocorticism, hypothyroidism, leishaminosis, neoplasia) or with immunosuppressive therapies (including glucocorticoids). However, despite thorough investigation, up to 50% of adult onset cases may not have an identifiable underlying disease. These cases have a guarded prognosis for relapse and at least some of these cases need lifelong therapy to remain controlled. In some cases demodicosis may precede identification of a subsequently developing systemic disease.

While the risk factors for short-bodied demodex demodicosis have not been well defined, the risk factors for *D. injai* demodicosis have been found to be different to that for *D. canis*. The mean age of diagnosis is later (mean 4.2-5.9 years), and terrier breeds are at higher risk for development of clinical disease, especially the West Highland white. In one study, there was a strong association with concurrent chronic disease (esp. atopic dermatitis) and prior immunosuppressive or immunomodulatory drug use. Whether these are independent risk factors or an epiphenomenon because of the at risk breeds is not known. Despite this, the author has noted cases in practice, moreso in younger dogs, with no obvious disease or drug association.

CLINICAL PRESENTATIONS & PATHOPHYSIOLOGY OF LESIONS

The primary lesions of demodicosis due to *D. canis* include spontaneous annular to regional partial to complete alopecia, scaling, follicular casts (keratosebaceous material adhered to the hair shaft), papules, pustules and comedones (blackheads). Other lesions include crusts, erythema, hyperpigmentation (esp. perfollicular), and lichenification. The head and forelegs are often but by no means always first affected. Lesions by definition do not affect non-follicular skin so pads and the planum should remain unaffected, and lightly haired regions (e.g. the ventral abdomen) are typically less affected. Secondary staphylococcal pyoderma is common and concurrent management is important. Management of the pyoderma without concurrent management of the mites may lead to partial or complete antibiotic treatment failure, and cases where this occurs should be a reminder to check for the presence of demodicosis.

D. canis demodicosis can occur with or without pruritus but pruritus is often very minor in the absence of concurrent secondary infections. Demodicosis complicated by the short-bodied form of the mite may show more scaling and pruritus.

Dogs with severe demodicosis involving furunculosis (follicular rupture) and concurrent deep pyoderma can present for evaluation of additional signs including swelling, pain, peripheral lymphadenopathy, lethargy, fever, and draining tracts. These cases associated with deep pyoderma, especially where *Pseudomonas* spp. are involved, can be a potential dermatologic emergency because of the risk of sepsis.

D. canis demodicosis can also present in a variety of atypical ways that the clinician needs to be aware of including:

- hot spots (especially non responsive superficial or deep types)
- focal granulomas and lichenified skin
- pustular rash
- pododermatitis without other body lesions
- otitis externa, typically waxy, crumbly (rarely alone, may be seen more commonly in combination with generalised demodicosis)
- comedones only
- mild crusting and scaling (esp. facial) without obvious hair loss (seen in longer-haired terrier dogs e.g. Scottish terrier and West Highland white)

D. injai infestations typically have a different presentation. They typically do not cause significant alopecia (though it can occasionally be noted) but instead are most commonly associated with an oily coat on the dorsum of the neck and trunk. In some cases this can be severe with dogs extremely oily again 24 hours after bathing. This clinical sign is consistent with the histological observation of sebaceous gland hyperplasia typical of this disease, and the mites can be observed in the sebaceous glands. Ordeix et al (2009) recently reported that not all cases of sebaceous hyperplasia resolve with successful treatment of the mites, raising the question as to whether the hyperplasia is a consequence of, or a prediposing factor for (or both) the mites. Other clinical signs variably noted in association with *D. injai* demodicosis include erythema, pruritus, scaling, and otitis. One abstract recently reported a presentation of intense facial pruritus, erythema, and variable hair loss and secondary infections in nine Shi Tzu dogs and one Scottish terrier. Anecdotally, it may also present as lip fold pyoderma, often poorly responsive to therapies.

Short-bodied demodicosis is considered to have scaling and variable hair loss as the predominant signs, and may be associated with pruritus. In the author's experience it is rarely seen without concurrent *D. canis*.

DIAGNOSIS

The most challenging aspect of some cases of canine demodicosis is simply the decision to take a sample to look for mites. At the author's practice, the number one cause for missed demodicosis diagnoses referred cases is failure to look for the mites, rather than the failure to find the mites on testing. However, once the decision has been made to look for *Demodex* spp. mites, there are various diagnostic options.

It is important to remember that although *Demodex* mites are part of the normal cutaneous flora in dogs, it is rare to find mites unless there is an overgrowth. A recent study (Fondati et al 2009) in healthy dogs using trichograms from five different body areas found 0/78 dogs positive for *D. canis* and a single adult *D. injai* from a labial commissure in 1/78 dogs. If low numbers (1-2 mites / slide) of *Demodex* mites are found on a skin scraping or hair pluck and clinical signs are not clear cut, then additional sites should be sampled. In most cases of clinical disease, finding mites should be reproducible and confirm the diagnosis. The exception to the rule is *D. injai* demodicosis. In that disease mites may be difficult to find even in clinically confirmed cases.

Skin Scrapings

Skin scrapings are the current 'gold standard' for mite diagnosis in most cases, with the best mite recovery of all techniques, assuming a correct sampling technique. Taking proper samples though can be a challenge with some patients, lesions and skin locations and in these cases sedation or use of other sampling techniques may be required. Skin scrapings can be performed with a No. 10 scalpel blade, though a No. 15 blade can be useful for small areas. To minimize the risk of a patient being injured during sampling the blade may be dulled first on a hard surface. Samples should be obtained from lesional skin and the skin can be squeezed before or during the scrapings to promote extrusion of *Demodex* mites from the hair follicles. Use of mineral oil will significantly aid in collection of the scraped sample, and the author tends to be generous in its use. It may be applied to the blade or the skin – just so long as it can be collected and placed on the slide! In a long- or medium-haired dog, gently clipping the area to be scraped will minimise the loss of the scraped material into the surrounding hair. Skin scrapings to identify follicular *Demodex* species mites need be deep enough to result in capillary bleeding.

Following transfer of the scraped material to a slide, a coverslip should be placed over the sample to ease examination and avoid contamination of the microscope objective with mineral oil. The author finds 50mm coverslips preferable and neater. To make the mites easier to find on examination (and this applies to all techniques below), lower the microscope condenser and decrease the light if required on the microscope to increase the contrast in the microscope field. Evaluating the scraped material with the 4X or 10X microscope objectives (40 or 100 times magnification) is sufficient. Microscope condensers should be racked down to improve contrast and mite visibility also. If there are low numbers of mites, evaluate the whole skin scraping for the total number of mites. If larger numbers of mites are present, estimate the number of mites per 100 times magnification field. Look for the presence and proportion of immature vs. adult mites. These figures should be recorded for each scrape site at each visit as with an effective treatment plan, a decreasing proportion of immature mite forms may be the first sign of improvement, and overall numbers and immatures should continue to drop with successful therapy. The presence of any mites—even dead mites or mite fragments—is considered a positive result when performing follow-up scrapings after commencing therapy.

Hair Plucks (Trichograms)

Hair plucks are less sensitive in diagnosing canine demodicosis compared with skin scrapings, but they are extraordinarily useful for areas of the skin that are difficult, such as the face and paws, or that may be too painful to scrape. Hair plucks can also be helpful if the sample area is already showing marked haemorrhage from ulceration or draining tracts because in these situations again it may be painful, and it may be difficult to determine how deep to scrape. Hair plucks may be performed with mosquito haemostat forceps to grasp and pull hairs, or fingers may be adequate. Ideally about 30-50 hairs per sample site should be adequate, and the key is to ensure the hair is removed with the root (rather than broken off) because this maximises the chance of the mites coming out with the hair. If alopecic lesions are being sampled, hairs should be collected from the lesion's margin. The skin may be squeezed before or during the hair plucks to promote mite extrusion from the follicles, but the author does not typically bother. The hairs should be placed on a glass slide with mineral oil, and to facilitate separation of the mites from the hair shafts and ease subsequent visualisation, the author 'chops' the hairs gently with the edge of the coverslip prior to its placement over the sample.

Exudative Samples

In cases of canine demodicosis with concurrent deep pyoderma, direct examination of the exudate from fistulous draining tracts may also reveal mites. Collect samples by squeezing the exudate onto a glass slide, and add mineral oil and a coverslip. In cases with follicular pustules, the pustules form in response to the mites, secondary bacterial infection or both. In any case, pustules make great lesions to sample. (The author wonders if indeed there is a case where pustules are ever not good to sample?) The top of the pustule can be carefully broken with a 25G needle and the contents transferred to a slide. If there is still exudate remaining in the pustule the short slide edge can be gently dragged over the pustule to express remaining exudate and collect it simultaneously. A squash technique is then appropriate for spreading the sample and both slides should then be examined prior to staining because the mites (which fail to uptake stain) are harder to observe over the background of stained inflammatory cells (and bacteria if present).

Sticky Tape Preparations

Acetate tape can be used to detect short-bodied *Demodex* spp., and occasionally *D. canis* or *D. injai* when present in sufficient numbers. The technique for this is to repeatedly press a piece of acetate tape to the skin and fur, and then lay the tape flat on a glass slide for microscopic examination unstained.

Otic Swabs

Demodectic otitis externa can be diagnosed by collecting samples from the ears with mineral oil soaked cotton swabs. Roll swabs and oil from each ear onto a glass slide and evaluate the slide after placing a coverslip. Alternatively, 'washing' of the ear with warm mineral oil, followed by removal of the oil with a soft tube and syringe is likely a more sensitive, though more demanding and messy technique.

Biopsy

Occasionally, an overgrowth of *D. canis* mites may be missed even with properly performed sampling methods, especially in dogs with thickened or fibrotic skin due to chronic dermatitis or because of their breed (*i.e.* Shar-Peis, bulldogs). If demodicosis is strongly suspected but no mites are found on skin scrapings and hair plucks, skin biopsy is recommended to evaluate for the presence of mites histologically. Multiple deep recuts should be requested on the histopathology request form as mites may not appear in every cut section of the biopsy.

Other Diagnostic Tests

Because of the drug and/or disease associations with adult-onset *D. canis* demodicosis and *D. injai* demodicosis, further tests may be required. A full physical examination and patient history (esp. thorough drug history) is mandatory in all cases. Cytology (tape, impression smear, exudative) for assessment of secondary infection is important, and consideration should be given to culture and sensitivity if *Pseudomonas* dermatitis or septicaemia is suspected. Thyroid assessment and ACTH stimulation tests in cases of adult onset disease should be considered but it is important to remember that both can give false positive reactions in the face of serious concurrent diseases, so these tests may be more reliable if left until the demodicosis and infections are under control. If testing is performed while demodicosis is still active, a normal result can be considered reliable (given the normal limitations of endocrine testing). Biochemistry and haematology should be considered where there is any suspicion of internal disease.

DIFFERENTIAL DIAGNOSES

The major clinical signs of canine demodicosis result from a folliculitis induced by the overgrowth of mites in the hair follicle. Any other dermatologic condition that results in inflammation of the hair follicle region will cause similar clinical signs. The major differential diagnoses for folliculitis include demodicosis, bacterial skin infection (bacterial folliculitis or superficial pyoderma), and much less commonly dermatophytosis. The greasy skin associated with *D. injai* may be mimicked by atopic dermatitis, which can be concurrent with the mites esp. in terrier breeds.

TREATMENT

Localised Demodicosis

Benign Neglect

In dogs, most cases of juvenile- onset localised demodicosis will spontaneously resolve. Many cases that fail to do so and spread are not localised disease at all, but generalised cases presenting at an early stage. Clinical and microscopic observation over several weeks with no mite-specific therapy is an option if signs are mild. If clinical signs progress or mite numbers increase, miticidal therapy is indicated.

Localised disease in adult dogs is unusual, and in the author's opinion an underlying disease should be looked for. If one is found and is able to be corrected then miticidal therapy may not be required, however, as with juvenile disease, if clinical signs progress or mite numbers increase, miticidal therapy is indicated.

Supportive Therapy

If infection is diagnosed, then management of this is important. It will also give the owner something to do when no miticidal therapy is being used. For a focal lesion consider 2% mupirucin (Bactroban) ointment bid, 0.05% chlorhexidine bid or 2.5% benzoyl peroxide gel (Benzac W2.5) bid (watch for irritation) until the lesions are clinically and cytologically cleared. For multifocal lesions systemic antibiotics should be considered (see below).

Miticidal Therapy

In mild cases Advocate q7-14d can be used. While this product is not the most potent miticidal therapy, it is safe, has good compliance and has a reasonable success rate in mild juvenile cases of demodicosis (see below). Amitraz has been recommended mixed in a 0.13-2% concentration with paraffin or mineral oil and applied every 1-3 days. The author does not recommend this off label use with the availability of other options.

Generalised Demodicosis

General Considerations

Generalised demodicosis can be a frustrating disease to treat. Owners should be counselled on the time (3 months at a minimum and rarely up to a year or longer) and commitment required to treat this occasionally life-threatening dermatosis. Premature cessation of therapy is the central reason for treatment failure. Since clinical signs often improve before parasitological cure, it is paramount owners understand the need for regularly scheduled follow-up visits to ensure a successful outcome. In adult-onset cases, long term treatment success is also directly related to identifying and controlling underlying conditions where possible – if these are not identified or controlled then relapse is probable. A client handout may be helpful in educating clients about this disease.

Despite the therapeutic challenge presented by some dogs with generalised demodicosis, some dogs less than 1 year of age with mild generalised disease may spontaneously recover, and recovery of *D. injai* demodicosis with treatment of only the underlying disease has been reported. In clinical practice though this author does normally risk not using miticidal therapies in the face of juvenile or adult-onset demodicosis.

Elective sterilisation in entire animals to avoid disease propagation in the gene pool (in young animals) and to avoid risk of relapse with subsequent oestrus in females should be discussed and can be performed once any secondary pyoderma is controlled. It should be noted though that the stress of anaesthesia and surgery may transiently promote disease progression.

Supportive Therapy

Superficial staphylococcal pyoderma is treated empirically by using a beta-lactamase-stable antibiotic (e.g. cephalexin 22mg/kg bid, clindamycin 5.5mg/kg bid, enrofloxacin 5mg/kg q24h) for a minimum of three weeks, and 7-14 days after cytological cure. In dogs with unresponsive superficial pyoderma or when rod-shaped bacteria are identified on cytological examination, consider selection of antibiotic therapy based on bacterial culture and antimicrobial sensitivity testing.

Adjunctive topical therapy with an antibacterial shampoo 1-2 times weekly may hasten clinical resolution though care needs to be taken so as to avoid reducing the miticidal efficacy of amitraz rinses if these are being used. Common antibacterial shampoo ingredients include benzoyl peroxide (e.g. Pyoben) and 3% chlorhexidine (e.g. Pyohex, Pyoderm S). Benzoyl peroxide-based shampoos are often recommended because of their keratolytic and supposed follicular flushing activity though this has not been substantiated, and they may irritate inflamed skin.

Miticidal Therapy

Irrespective of the particular miticidal therapy being used, the author will always treat for 2 months past the point where mites are able to be found. As the numbers of mites decrease, the remaining mites become harder to find. Given that we only scrape (conservatively) 0.1% of a dog’s skin surface area, it is probable that by the time the first negative skin scrape has been achieved that there are still likely low numbers of mites present. By treating for a significant period past this point, the possibility of stopping treatment prematurely is minimised.

Amitraz

Topical amitraz is approved for treating generalised demodicosis in dogs older than 4 months of age. Amitraz, a miticide and insecticide, is a monoamine oxidase inhibitor (MAOI), prostaglandin synthesis inhibitor, and an alpha$_2$-adrenergic agonist. As per the product label, amitraz liquid concentrate (Demadex – Delvet) is to be used as a 10ml per litre of water dip every week. Efficacy of amitraz dips is maximised by:

- Clipping long and medium-haired dogs
- Removing crusts with shampooing prior to dipping (though ideally leaving to dry first to avoid dilution of the amitraz)
- Allow the dog to stand in run off solution to treat the paws
- Prevent wetting between dips.

Not all dogs can be cured with amitraz administered per the label protocol, though some cases apparently resistant to the macrocyclic lactones can respond to amitraz.

Amitraz dips are not without risk to dogs and their handlers. Many patients experience mild toxicosis seen as excessive lethargy for one or two days after dipping. This may be avoided in some patients by washing alternate body halves to reduce exposure. Vomiting, diarrhoea, polyuria and polydipsia have also been reported. More overt signs of toxicosis are similar to those seen with the use of alpha$_2$-adrenergic agonists, including sedation, ataxia, hypothermia, bradycardia and hyperglycaemia. Hyperglycaemia is a potential concern in diabetic dogs and clients. The use of alpha$_2$-adrenergic antagonists can reverse signs of toxicosis and can be used before dipping in patients with a history of adverse effects. Atipamezole (Antisedan, 50 µg/kg intramuscularly) can reverse the signs of toxicosis within 10 minutes. Avoid antidepressants and MAOIs, such as selegiline, in dogs receiving amitraz. Animal handlers administering amitraz should wear protective clothing and apply it in a well-ventilated area. Personnel should be aware of the potential risk for drug interactions. Those with respiratory problems or diabetes should not use amitraz.

A new spot-on formulation containing metaflumizone and amitraz (ProMeris—Fort Dodge Animal Health) is available in the United States (and may become available in Australia) to control fleas and ticks on dogs. It is recommended to be used monthly for the treatment of generalised demodicosis though one study has used it every two weeks. In that study, 92.3% of juvenile-onset cases were mite-free within 90 days, but only 45.4% of adult-onset cases.

Long term follow-up has not been performed in any study with this product as yet. Side effects included uncommonly vomiting, diarrhoea, transient lethargy, and rarely a specific pemphigus foliaceous-like drug eruption. The product itself has a strong odour requiring outdoor application. More critically evaluated trials are needed to substantiate this drug's efficacy in the long-term control of generalised demodicosis.

Ivermectin

Macrocyclic lactones include the avermectins (ivermectin and doramectin) and milbemycins (milbemycin oxime and moxidectin). This class of drugs selectively binds to glutamate-gated and gamma-aminobutyric acid (GABA)-gated chloride channels in the mite's nervous system, resulting in cell hyperpolarisation, mite paralysis, and finally, death. Macrocyclic lactones do not readily cross the mature mammalian blood-brain barrier. Safety in mammals is due to the lack of glutamate-gated chloride channels in the peripheral nervous system and the restriction of GABA to the central nervous system.

The ease of oral administration compared with dips, reliability in efficacy and relative safety makes macrocyclic lactones the first line of therapy for many dermatologists including the author. Unfortunately, the use of macrocyclic lactones for generalised demodicosis is extralabel, and there is no antidote to the potentially serious and life-threatening side effects. Ideally, dogs should have negative heartworm disease test results before macrocyclic lactone therapy is implemented. When using macrocyclic lactones for generalised demodicosis, the owner must understand their extralabel use and potential for side effects.

For generalised demodicosis, the injectable form of ivermectin is given orally at a dose of 300-600 µg/kg/day. The author tends to start at 300µg/kg daily and if improvement does not occur, or improvement plateaus for 8 weeks will increase the dose to 600µg/kg. If this fails to decrease mite counts further then alternative therapies need to be considered including milbemycin oxime, doramectin or amitraz. The aqueous formulations may be more palatable than the propylene glycol-based products though studies of different pharmacokinetics of these different formulations have not been performed in dogs. To minimise the risk of severe toxicity associated with ivermectin in individual cases, ivermectin should be dosed initially at 50 µg/kg/day and then the dose increased each day by 50 µg/kg daily until the target dose is achieved. The goal with this is to not significantly overdose sensitive individuals and cause severe toxicity. In one study using a similar protocol, 2/222 dogs showed signs of ivermectin toxicity that resolved with only cessation of medication.

The pour-on formulation of ivermectin is not effective in treating generalized demodicosis, and injections have proven unreliable.

Adverse events are sporadic and include lethargy and rarely oedematous wheals, but the main concern is the development of signs attributable to severe neurotoxicosis including mydriasis, muscle tremors, lethargy, stupor, coma, ataxia, and rarely seizures; death can also result. Blindness has also been rarely reported in dogs though this has not been seen at ASEAC.

Signs of ivermectin toxicosis can occur in any breed but are most reported in ivermectin-sensitive breeds. Doses in ivermectin-sensitive dogs causing toxicosis have generally exceeded 100µg/kg but there is a single report of an ivermectin-sensitive breed presenting with signs of toxicosis at a dose less than this. In non-ivermectin sensitive dogs, the dosage required to cause toxicosis is generally much higher (greater than 3500µg/kg) but cases have been reported showing adverse signs at doses less than 2500µg/kg.

Ivermectin sensitivity is derived from a mutation of the multidrug resistance gene (MDR1; though the most recent nomenclature is ABCB1). The product of the MDR1 gene, P-glycoprotein, is a large ATP-dependent transmembrane protein transporter found in the blood-brain barrier and other tissues. P-glycoprotein (P-gp) pumps substrates (e.g. ivermectin and loperamide) within the brain back into the blood thereby limiting uptake by the central nervous system. Dogs homozygous for this mutation (ABCB1-1Δ) display an ivermectin-sensitive phenotype, developing severe neurotoxicosis after a single dose of ivermectin (as low as 100µg/kg and very rarely 50 µg/kg). When ivermectin is deemed necessary for a dog (and ideally this should be in all cases though this is not always feasible for all clients), testing for the ABCB 1-1Δ genotype before its use is available through Gribbles Pathology. Breeds where the mutation has been identified in the US and Europe include normal and miniature Australian Shepherds, Collies, English Shepherds, longhaired Whippets, Old English Sheepdogs, Shetland Sheepdogs, German Shepherds and Silken Windhounds. Border Collies were identified with the mutation but with a frequency less than that of mixed breed dogs suggesting the mutation is very rare in this breed. One clinical study suggests greyhounds may also be at increased risk. In Australia, only 12% of Collies, 36% of Australian Shepherds and 43% of Shetland Sheepdogs were homozygous for the normal allele though numbers tested were low. 7/7 Border Collies were homozygous for the normal allele in that study.

Dogs without an ivermectin-sensitive genotype can potentially still show signs of toxicosis if ivermectin is given in conjunction with P-gp inhibitors (e.g. cyclosporin, fluoxetine, ketoconazole, itraconazole, methadone, other macrocyclic lactones including selamectin, and others). Furthermore, spinosad (Comfortis, Elanco) may potentiate ivermectin toxicity (mydriasis, hypersalivation, lethargy, ataxia, trembling, etc) where ivermectin is being used at a high dose. Clinical signs typically start within 4-6 hours of receiving the spinosad in conjunction with off-label ivermectin use. These problems were not noted with concurrent use of spinosad in conjunction with high doses of milbemycin in ivermectin-sensitive collies. Elanco has advised that a veterinarian waits for at least 15 days, preferably 30 days following the end of any dose of avermectin or milbemycin therapy over and above the normal heartworm preventative dose before administering Comfortis as there is not enough data currently to establish the dose at which the safety break point occurs for ivermectin and no information regarding other macrocyclic lactones at high doses.

Subacute toxicity has also been reported following several weeks to months of ivermectin therapy. This is unassociated with MDR1 mutations, unassociated with specific breeds, has been reported both with and without concurrent use of other P-gp substrates, and may be a consequence of the slow increase in ivermectin (which has a long half life) serum concentrations with daily dosing.

Thus, patients of all breeds need to be monitored for side effects at all times while on therapy, but especially in the first 2-3 months.

Doramectin

There is fair evidence to recommend use of doramectin as a weekly injectable at 600 µg/kg SC. It has also been used at 300µg/kg PO eod in a small study, and in the author's practice it has been used 600µg/kg twice weekly PO. Side effects similar to ivermectin are possible in ivermectin-sensitive dogs and a twice weekly build-up starting at 50-100 µg/kg to help identify these dogs has been used by the author similar to the ivermectin build-up.

Milbemycin Oxime

There is good evidence to recommend milbemycin oxime at 2mg/kg daily for the treatment of generalised demodicosis. Milbemycin oxime can cause adverse reactions at effective doses in ivermectin-sensitive dogs. However, these side effects have been limited to ataxia rather than severe depression and coma, so it appears the safety margin for this therapy is much greater. Price and availability without other endocides are a barrier to regular use.

Moxidectin

Moxidectin has been used with good evidence for success in adult- and juvenile-onset demodicosis at 400µg/kg PO daily. Side effects are similar to ivermectin although a single case of a known homozygous MDR-1 positive dog showed milder signs of ataxia, crawling, acoustic and tactile hyperexcitability, and miosis after a single 400µg/kg dose of moxidectin, suggesting that the side effects associated with this drug in ivermectin-sensitive dogs may not be as severe as ivermectin. That the potency of moxidectin P-gp function was 10 times lower than other macrocyclic lactones in one study supports this possibility. Further clinical studies are warranted.

Advocate (imidacloprid, moxidectin) is registered for treatment of demodectic mange with monthly application. Recent studies however find much better response with fortnightly dosing, and better response again with weekly dosing. No side effects have been reported in studies with frequency of dosing. In the study examining fortnightly dosing, a significantly better response rate was seen in milder cases, and also in juvenile onset cases compared with adult-onset cases. With an overall remission rate of 43.3% when used fortnightly, Advocate remains an imperfect choice for treatment of demodectic mange but its safety, compliance and better response again with weekly dosing suggests that it may be a treatment option in milder cases of juvenile-onset demodicosis.

WHEN THINGS GO WRONG: REASONS FOR (APPARENT AND ACTUAL) TREATMENT FAILURE

Failure to Control Concurrent Infection

Even if mites are successfully treated if infection is left untreated then significant skin lesions may remain. Cytology should be repeated to identify infection and adequate antibiotic therapy instituted.

Failure to Select Miticidal Medication at the Correct Dose for Correct Length of Time

Mistakes can be made in initial calculations of macrocyclic lactone doses, and where juvenile-onset cases are treated, the growth of the patient may result in a relative underdosing over time. Premature cessation of therapy (i.e. less than 1-2 months after parasitological cure) increases the risk of relapse.

Compliance Failure

Failure of client compliance with dosing will, not surprisingly, reduce the chance of successful treatment. Especially where amitraz is being used, correct dilution and application is essential. With the macrocyclic lactones, calculating the dose that should have been used and comparing this with the actual amount used may reveal otherwise undetected compliance failures.

Inappropriate Storage of Miticide

Most of the miticides have strict storage requirements, esp. ivermectin which is UV sensitive and can degrade if not stored out of the light. Querying clients and ensuring correct storage should avoid this problem.

Failure to Monitor the Patient

Regular patient monitoring is imperative to ensure mite numbers continue to reduce, infection remains controlled and treatment continues for the full course. With clinical improvement it is not uncommon for clients to want to stop therapy prematurely as they perceive a clinical cure is equivalent to a parasitological cure. Regular follow-ups help ensure correct duration of dosage, and will detect any problems in therapy before they become too problematic.

Failure to Avoid Use of Glucocorticoids or Other Immunosuppressive Therapies

Concurrent use of immunosuppressive medications may make clearing the mites more difficult, and in some cases prevent full parasitological cure necessitating long term therapy to control mite numbers. In some cases cessation of immunosuppressive therapies is not possible because of treatment of concurrent disease and client should be made aware of the possible consequences of this early in the treatment course.

Failure to Identify and Treat Underlying Diseases

In dogs with adult-onset disease especially, a failure to identify and treat the underlying trigger can significantly increase the risk of relapse, and sometimes prevent a parasitological cure. In idiopathic adult-onset cases where an underlying disease cannot be isolated despite diagnostic attempts to do so, a guarded prognosis should be given for long term relapse.

Fibrosis Entrapping Mites

In severe cases of demodicosis (and more often in cases complicated by glucocorticoid use in the author's opinion), mites can become encased in dermal fibrosis. These mites are difficult to reach with miticides, and even if dead, are likely to remain trapped in the dermis, with the potential to trigger ongoing inflammation.

'Resistance' to the Miticide

Some cases simply do not respond to appropriate medications given at appropriate doses. Whether these cases have innate or acquired resistance to the miticide, or whether there is individual pharmacological variation in achieving appropriate therapeutic levels of miticide is difficult to prove. In these cases, moving to a different drug (doramectin has been reported useful in some apparently ivermectin-resistant cases), macrocyclic lactone family (avermectin instead of milbemycin or vice versa), or drug group altogether (amitraz for macrocyclic lactone or vice versa) may be beneficial.

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NOTES:

Chapter 30

Zoo Animal Dermatology: An Exercise in First Principles Workups

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CASE 1

Signalment:

4 year old, male, Rothschild giraffe

Presenting History:

Developed perineal papules and pruritus in Aug 2001. Responded in part to Sebolyse washes. March 2002 developed urticarial type reactions on the legs and increased perineal lesions + stiffness in the joints. Poor response to antibiotics (in that the lesions progressed to 1/2 moon shaped areas of epilation and "eschar" formation. The swellings on the limbs have settled. The gait improved after a dexamethasone injection. Currently (June 2002) there is active disease again with scratching.

Process (es)?

Differential Diagnosis

Diagnostic Work Up

Diagnosis and Outcome

CASE 2

Signalment:

Adult, female, Black Rhino.

Presenting History;

Facial and rump pruritus, excoriation, scaling and fly irritation.

Process (es)?

Differential Diagnosis

Diagnostic Work Up

Diagnosis and Outcome

CASE 3

Signalment:

9 year old, male, Eurasian badger

Presenting History

Progressive alopecia face and flanks. Flank skin non-inflamed, mild erythema and scaling around face.

Process (es)?

Differential Diagnosis

Diagnostic Work Up

Diagnosis and Outcome

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Chapter 31

Interactive Case Sessions: Biopsies & Advances in Dermatology

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* equivalent to a fully compliant daily, oral antibiotic regimen prescribed for common skin and soft tissue infections (SSTI) and urinary tract infections (UTI).

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